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META-ANALYSIS OPEN ACCESS

Meta-Analysis: Effects of Steatotic Liver Disease-Associated Genetic Risk Alleles on Longitudinal Outcomes

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ABSTRACT

Background: Genetic variants associated with risk of steatotic liver disease (SLD) may also influence clinical events.

Aims: To perform a systematic review and meta-analysis to determine the impact of SLD-associated genetic variants on hepatic and extrahepatic complications in SLD.

Methods: We searched PubMed, Embase and Medline databases from inception through July 4th, 2024 for studies on adults with SLD that reported effects of *PNPLA3*, *TM6SF2*, *MBOAT7*, *HSD17B13* and *GCKR* variants on the incidence of cirrhosis, major adverse liver outcomes (MALO), cardiovascular disease, extrahepatic malignancy and overall or cause-specific mortality. We pooled hazard ratios and 95% confidence intervals from these outcomes to allow for comparison.

Results: We screened 6475 studies and included 40 in the final analysis. *PNPLA3*-rs738409-GG genotype (vs. CC genotype) was associated with significantly higher incidence of MALO (sHR 2.30 [95% CI 1.66–3.18]), liver-related mortality (sHR 2.83 [95%

Abbreviations: ALD, alcohol-associated liver disease; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; FIB-4, fibrosis-4 index; HCC, hepatocellular carcinoma; HR, hazard ratio; MALO, major adverse liver outcomes; MASLD, metabolic dysfunction-associated steatotic liver disease; sHR, subhazard ratio; SLD, steatotic liver disease.

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CI 1.58–5.06]) and all-cause mortality (HR 1.24 [95% CI 1.04–1.47]). *TM6SF2*-rs58542926-CT or TT (vs. CC) genotype was associated with a higher incidence of hepatocellular carcinoma (sHR 2.12 [95% CI 1.66–2.70]). MALO was significantly associated with *MBOAT7* -rs641738-TT (vs. CC) genotype (sHR 1.21 [95% CI 1.1–1.33]). Limitations in the literature include inconsistent outcome reporting and distribution of fibrosis stage, and a relative paucity of studies on both alcohol-associated liver disease and non-*PNPLA3* genetic variants.

Conclusions: Variants in *PNPLA3*, *TM6SF2* and *MBOAT7* are significantly associated with hepatic outcomes, especially with advanced baseline liver disease, with modest effects on extrahepatic outcomes. Routine genotyping may improve risk stratification in SLD patients with advanced liver disease.

1 | Introduction

Chronic liver disease is a major cause of morbidity and mortality, causing approximately two million deaths annually [1]. Steatotic liver disease (SLD), comprising metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD), is the leading and most rapidly rising cause of death from chronic liver disease [1, 2].

The development of steatosis and the rate at which inflammation progresses is a multifactorial process that results from a complex interplay of genetic and epigenetic susceptibility, behavioural risk factors and metabolic comorbidities [3, 4]. Genetic variants in/near *PNPLA3*, *TM6SF2*, *MBOAT7*, *HSD17B13* and *GCKR* have been associated with SLD presence and severity, with substantial overlap between MASLD- and ALD-promoting variants [5–11]. Specific risk variants in/near these genes have been associated with hepatic fat deposition, as well as the progression to cirrhosis and resultant sequelae, including decompensation, hepatocellular carcinoma (HCC) development and mortality [12].

Most of the literature on SLD-promoting genetic variants has included case–control studies. In contrast, there is more limited literature on how these variants affect longitudinal outcomes. Variants in *PNPLA3* have consistently been shown to increase the risk of major adverse liver outcomes (MALO) including hepatic decompensation and HCC, but the true effect size is unclear [13]. The effects of other variants on MALO are less well described. There also remains controversy in the literature about the impact of SLD-promoting genetic variants on cardiovascular outcomes [14, 15] or overall mortality [12, 16]. Identifying patients with higher risk genotypes could aid risk stratification in SLD in terms of both liver-related and extrahepatic complications and aid with tailoring management strategies based on risk of progression [17, 18].

Here, we performed a systematic review and meta-analysis to determine the impact of SLD-associated genetic variants on both hepatic and extrahepatic complications as well as overall and cause-specific mortality in SLD.

2 | Methods

2.1 | Search Strategy

We searched PubMed (via Pubmed.gov), MEDLINE (All) and Embase.com (including Embase Classic) databases from inception through July 4th, 2024 to identify potential articles for inclusion (Table S1). Following the initial search, the abstracts of all studies were reviewed for relevance to our clinical question. This study was reported in accordance with the PRISMA guidelines (Figure S1). Our systematic review protocol was registered in Prospero for review prior to publication (Prospero ID CRD420251010855).

2.2 | Selection and Eligibility Criteria

Studies were included in the final analysis if they met the following criteria: (1) included adults (≥18 years) with steatotic liver disease; (2) evaluated the impact of a lead variant in one of the best-established SLD-associated genes (*PNPLA3*-rs738409, *TM6SF2*-rs58542926, *HSD17B13*-rs72613567 or rs6834314, *MBOAT7*-rs641738 and *GCKR*-rs1260326) (Table 1); and (3) reported impact on longitudinal endpoints using time to event metrics, including hazard ratios, incidence rates, or cumulative incidence. Included outcomes were incident cirrhosis/advanced liver disease (defined as diagnosed cirrhosis with or without decompensation or HCC), HCC, MALO (typically defined as decompensation with ascites, variceal bleeding, or hepatic encephalopathy, or HCC), cardiovascular disease (CVD), extrahepatic cancer, liver-related mortality, CVD-related mortality and all-cause mortality. Studies that combined participants with SLD and those with other etiologies were included if the effects of genotypes were separately reported for the participants with SLD. Studies with only cross-sectional or case–control analyses were excluded, as were those other including paediatric patients or written in languages other than English. Study eligibility was evaluated independently by at least two investigators (MK, EQ, JT). In case of conflicting opinions, the third investigator would determine the decision. Two independent reviewers (MK, VP) verified the quality of each study using the Q-genie assessment (Table S2) [32]. If their scores differed by no more than 1 point, the mean of the two reviewers' scores was used. Otherwise, scores were adjudicated by a third reviewer (VC) whose score was used as the final score. The investigators also verified the quality of each evidence and risk bias using the GRADE system (Table S3) [33].

2.3 | Data Extraction

Following the exclusion of irrelevant studies, authors independently reviewed the included studies to extract the relevant data to be used for inclusion in the final analysis. Data that was extracted including (1) study characteristics: author, year of publication, journal, study design, country study was performed, years of recruitment, genes examined, aetiology of liver disease,

TABLE 1 | Genetic variant information.

Gene	Variant	Effect allele	Other allele	Effect allele frequency	Presumed function of gene	Presumed effects of genetic variant
PNPLA3	rs738409 chr22:43928847	G	C	G = 0.215 EUR: 0.213 AFR: 0.0898 EAS: 0.403	Triacylglycerol lipase, preferentially hydrolyzes polyunsaturated triglycerides [19]	I148M mutation increases PNPLA3 interference with adipose triglyceride lipase (ATGL/CGI-58) resulting in increased triglyceride accumulation in hepatocytes and adipocytes [20, 21]
TM6SF2	rs58542926 chr19:19268740	T	C	T = 0.0685 EUR: 0.0738 AFR: 0.0338 EAS: 0.0737	Regulates triglyceride secretion: increases triglyceride secretion [22, 23]	Loss of function [24, 25]
HSD17B13	rs72613567 chr4:87310241	TA	T	TA = 0.224 EUR: 0.248 AFR: 0.0856 EAS: 0.355	Retinol dehydrogenase [5, 8]	rs72613567-TA is a splice variant resulting in exon 6 skipping and loss of function [5, 8]. rs6834314-G is a non-coding variant in strong linkage disequilibrium with rs72613567; this variant has no known independent significance
	rs6834314 chr4:87292656	G	A	G = 0.248 EUR: 0.259 AFR: 0.222 EAS: 0.38		
MBOAT7	rs641738 chr19:54173068	T	C	T = 0.436 EUR: 0.436 AFR: 0.344 EAS: 0.235	Lysophosphatidylinositol acyltransferase involved in phospholipid remodelling [26]	rs641738-T results in decreased expression of MBOAT7 and changes in phospholipid profiles [6, 27]
GCKR	rs1260326 chr2:27508073	T	C	T = 0.409 EUR: 0.420 AFR: 0.151 EAS: 0.529	Codes for glucokinase regulatory protein (GKRP) which inhibits glucokinase (first step in glycolysis) [28]	Impaired binding of GKRP to glucokinase, thus increasing hepatic conversion of glucose to triglycerides [29–31]

Note: Allele frequencies, chromosome: position, effect/other alleles and allele frequencies were obtained from dbSNP (https://www.ncbi.nlm.nih.gov/snp, accessed May 12, 2025). Chromosome: position are based on Genome Reference Consortium, build 38, patch release 14.
Abbreviations: AFR, African ancestry; EAS, East Asian ancestry; EUR, European ancestry.

time of follow-up, confounders adjusted for analysis; (2) patient data: sample size, average age, gender, ethnicity, BMI, comorbidities, MASLD diagnostic criteria, average alcohol consumption data, fibrosis assessment criteria; and (3) outcomes as detailed above. Outcomes were collected according to the respective genetic variant being examined. Additionally, outcomes stratified by fibrosis stratification were collected if reported.

2.4 | Statistical Analysis

Data analysis was conducted using R studio (Version 1.4.1564) for all forest plots. Statistical heterogeneity was assessed using Cochran's Q test, supplemented by I^2 statistics to quantify the proportion of total variation across studies attributable to heterogeneity rather than chance. I^2 values categorise heterogeneity as may not be important (0%–25%), low (26%–50%), moderate (51%–75%), or high (> 75%). A random-effects model was used in all analyses due to the heterogeneous background populations and protocols among the studies. Note that the *HSD17B13*-rs72613567-TA (splice variant) and rs6834314-G were pooled for all analyses given high linkage disequilibrium ($r^2 = 0.94$) [5, 8]. Instead of analysing the effect of each variant separately, the effects of both variants are pooled together as if they represent a single genetic factor. We only conducted meta-analysis of outcomes in studies that reported hazard ratios; we meta-analysed the most commonly reported comparisons (e.g., *PNPLA3*-rs738409-GG vs. CC). When multiple studies utilised the same cohort (e.g., UK Biobank), the study using the larger subset of that cohort was used for meta-analysis. We employed the generic inverse variance method of DerSimonian and Laird to calculate pooled effect estimates by combining point estimates and their associated standard errors extracted from each study [34]. The pooled HR and 95% confidence interval (CI) were then calculated for each outcome by combining the HR of each study using a random-effects model. Some studies reported HR while others reported subhazard ratios (sHR); we meta-analysed these together but reported all-cause mortality outcomes by HR and others by sHR. Subgroup analysis of clinical outcomes was stratified based on the diagnostic method, presence of only MASLD, presence of only ALD, adjusted HR, sHR and the region where the studies were conducted. Subgroup differences were used to determine if there was a statistically significant difference in clinical characteristics between groups. A two-tailed p-value < 0.05 was considered the threshold for statistical significance.

3 | Results

3.1 | Literature Search

Our search yielded a total of 6475 titles, with 2891 duplicates identified by the computer-assisted software and 84 additional duplicates detected during the screening process by the reviewers, resulting in 3500 unique studies at initial screening. After initial screening to exclude studies that were either irrelevant or did not fit the inclusion criteria based on review of the title and abstract, 232 were included in the full-text review. These studies were reviewed, and studies that did not fit the inclusion criteria, such as those that did not examine longitudinal outcomes or use time-to-event analyses, or studies that included patients without liver disease or non-steatotic liver disease, were excluded. After full-text review, 40 studies were included in the systematic review. (Figure S1).

3.2 | PNPLA3-rs738409

3.2.1 | Major Adverse Liver Outcomes

There were 19 cohorts (18 studies) with 270,833 participants that assessed the association between *PNPLA3*-rs738409-G allele (corresponding to p.Ile148Met protein mutation) and MALO [12, 15, 16, 35–49] (Table 2) (Figure 1). Of these studies, 15 studies [12, 15, 16, 35–38, 40–42, 44, 46, 47, 49] reported that *PNPLA3*-rs738409-G allele was associated with increased risk (four comparing per G-allele, six comparing GG vs. CC, three comparing both CG and GG vs. CC, one comparing GG vs. CC/CG and one comparing CG/GG vs. CC), and four studies [39, 43, 45, 48] with no difference. We included eight studies that reported effects of rs738409-GG versus -CC genotype in the meta-analysis. Pooled sHR for these studies was 2.30 (95% CI 1.66, 3.18) for rs738409-GG versus -CC (Figure 2A). The meta-analysis had a moderate heterogeneity with I^2 of 59.2%.

3.2.2 | Hepatocellular Carcinoma

There were 11 studies with 167,244 participants that assessed the association between *PNPLA3* and HCC incidence [38, 42, 45, 46, 50–56] (Table 2). Of these studies, five studies [38, 42, 46, 50, 56] reported that *PNPLA3*-rs738409-G allele was associated with increased risk (one comparing per G-allele, two comparing GG vs. CC, one comparing both CG and GG vs. CC, and one comparing CC/CG vs. GG), and six studies [45, 51–55] with no difference. Among the three studies that could be included in the meta-analysis, pooled sHR was 2.18 (95% CI 1.46, 3.27) for rs738409-GG versus -CC (Figure S2A). The meta-analysis had a low heterogeneity with I^2 of 36.8%.

3.2.3 | Cirrhosis/Advanced Liver Disease

There were nine cohorts (eight studies) with 262,229 participants that assessed the association between *PNPLA3* and incidence of cirrhosis or advanced liver disease (typically defined as cirrhosis with or without decompensation or HCC) [36, 42, 43, 49, 54, 59–61] (Table S4). Of these studies, in seven cohorts [36, 42, 43, 49, 54, 61] *PNPLA3*-rs738409-G allele was associated with increased risk (three comparing per G-allele, three comparing GG vs. CC, and one comparing both CG and GG vs. CC), and in two [59, 60] with no difference. Among the three studies that could be included in the meta-analysis, pooled sHR was 2.47 (95% CI 1.81, 3.37) for rs738409-GG versus -CC (Figure S2B). The meta-analysis had a low heterogeneity with I^2 of 44.6%.

3.2.4 | Liver-Related Mortality

Five studies with 8195 participants assessed the association between *PNPLA3* and liver-related mortality [16, 38, 46, 57, 58]

TABLE 2 | *PNPLA3* liver-related outcomes.

Study	Steatosis criteria	Cohort type	Cohort	Fibrosis stage	Outcome definition	Findings
MALO						
Armisen 2023 [35]	Biopsy	Medical centre	$N = 1686$, MASLD 100%, Age: 48, Male 29%, Hispanic/Latino 2%, BMI: 42.3, DM 39%, Follow-up: NA	Fibrosis stage: 0 (44%), 1 (34%), 2 (9%), 3 (9%), 4 (5%)	Cirrhosis, decompensated cirrhosis, HCC, liver failure and transplantation	PNPLA3-rs738409-GG risk allele increases risk of ESLD outcomes independent of degree of fibrosis ($p = 0.05$)
Chalasani 2024 [12]	Biopsy	Medical centre	$N = 2075$, MASLD 100%, Age 50.4, Male 37.5%, White 74.8%, Black 3.0%, Hispanic 11.6%, Asian 6.0%, Other 4.5%, BMI: 34.4 DM 36.1%, Follow-up: Mean 4.3 years	Biopsy fibrosis stages: 0: 25.1%, 1: 26.6%, 2: 18.8%, 3: 20.0%, 4: 9.5%	Liver-specific death or transplant, HCC, or new onset GE varices or hepatic decompensation, including ascites, HE, or variceal bleeding	G-risk allele: unadjusted/crude HR: 1.18 (0.92–1.51); Adj. sHR: 1.39 (1.07–1.82) CG: crude HR: 1.37 (0.85–2.21); Adj. sHR: 1.51 (0.92–2.4) GG: crude HR: 1.40 (0.83–2.37); Adj. sHR: 1.94 (1.12–3.37)
Chen 2022 (MGI) [36]	Labs, ICD codes	Medical centre	$N = 7893$, MASLD 100%, Age 52.3, Male 43.1%, White 85.8%, Black 5.8%, Asian 3.1%, Other 2.2%, BMI: lean 15.4, overweight 26.6, obese class I 26.5, obese class II 16.5, obese class III 14.9 DM 35.5%, Follow-up: Median 71.6 months	FIB-4: < 1.3 (54.7), 1.3–2.67 (38.9), > 2.67 (6.3)	Hepatic decompensation or HCC based on ICD codes	GG vs. CC: HR 3.51 (1.91–6.46), $p < 0.0001$ CG vs. CC: 1.40 (0.87–2.27) $p = 0.16$. Overlap with Miller 2023 and Wijarnpreecha 2023.
Chen 2022 (UKBB) [36]	Labs or ICD code	Community	$N = 46{,}880$, MASLD 100%, Age 55.6, Male 52.0% White 93.9%, Black 1.3%, Asian 2.6%, Other 2.2% BMI: lean 23.3, overweight 40.5, obese class I 31.6, obese class II 10.6, obese class III 4.0 DM 9.7%, Follow-up: Median 106.3 months	FIB-4: < 1.3 (45.3), 1.3–2.67 (50.8), > 2.67 (3.8)	ICD codes for cirrhosis or portal hypertensive complications	CG vs. CC: HR 1.05 (0.80–1.38) $p = 0.73$ GG vs. CC: HR 1.99 (1.38–2.88) $p = 0.00024$

(Continues)

TABLE 2 | (Continued)

Study	Steatosis criteria	Cohort type	Cohort	Fibrosis stage	Outcome definition	Findings
Friedrich 2014 [37]	Clinical discretion	Medical centre	*N* = 105, ALD 100%, Age: 52.6, Male: 74.3%, White: 100%, BMI: 26.7, Follow-up: NA	All patients with ESLD	Decompensation requiring paracentesis or diuretic treatment, SBP, HE, or HRS	Cumulative incidence: CC: 18.3 months ±3.6 (95% CI: 11.2–25.4); CG/GG: 12.71 months ±3.5, (95% CI: 5.7–19.7) $p = 0.04$
Grimaudo 2020 [38]	Biopsy or ultrasound with 1 criterion of metabolic syndrome	Medical centre	*N* = 471, MASLD 100%, Age 49.4, Male 61.6%, Italian: 100% (assumed), BMI: 30.3, DM: 46.1%, Follow-up: Median 64.6 months	Fibrosis stage 3–4 on biopsy: 34.5%	Liver decompensation: ascites, bleeding varices, encephalopathy, jaundice, or HCC	G-variant: univariate HR 1.93 (1.13–3.30) $p = 0.01$; multivariate: HR 2.10 (1.03–4.29) $p = 0.04$
Holmer 2022 [15]	Imaging/biopsy	Medical centre	*N* = 547, MASLD 100%, Age median 51, Swedish: 100% (assumed), Male 62%, BMI 27.4, DM 19.1%, Follow-up: Median 19.6 years	Fibrosis stage %: 0 (24.6), 1 (38.7), 2 (22.2), 3 (10.3), 4 (4.2)	Diagnosis of cirrhosis, decompensation with ascites, GE varices, HE, portal hypertension, HRS or HCC	GG vs. CC: crude analysis (HR 2.14, 95% CI = 1.17–3.91); adjusted for age, sex, DM and BMI (aHR 2.27, 95% CI = 1.15–4.47)
Iwaki 2022 [39]	Biopsy	Medical centre	*N* = 223, MASLD 100%, Age: 52.1, Male: 51%, Japanese: 100% (assumed), BMI: 27.9, DM: 23.4%, Follow-up: Median 8.9 years	Mean FIB-4: 1.5	Cardiovascular events, liver-related events (composite endpoint of GE varices/bleeding, HCC, or decompensated cirrhosis) and extrahepatic cancers	GG vs. CC/CG: HR 1.43 (0.28–7.2) $p = 0.66$
Kocas-Kilicarslan 2024 [40]	Imaging	Medical centre	*N* = 217, MASLD 100%, Age 54.7, Male 36.4%, White: 61.7% African American: 2.7%, Hispanic: 0%, Asian: 1.5%, Other: 0.9%, No data: 69.44%, BMI: 34.0, DM: 42.9%, Follow-up: NA	Not available	Progression to ESLD	G-allele carriers: RRR 2.558 (1.521–4.304) $p = 0.000$
Lavrado 2024 [41]	Steatosis on ultrasonography	Medical centre	*N* = 407, MASLD 100%, Age 62.1, Male 32.4%, Brazilian: 100% (assumed), BMI: 31.5, DM 100%, Follow-up: Median 11 years	Elastography: Liver stiffness: 6.3 kPa; CAP: 291.6	Cirrhosis complications registered were HCC and oesophageal/gastric varices, with or without previous bleeding	GG v CC: Crude/unadjusted: HR 14.15 (4.26–47.08) $p < 0.001$; age, sex-adjusted: HR 14.17 (4.23–47.42) $p < 0.001$; multivariable adjusted: HR 16.83 (4.51–62.86) $p = < 0.001$

(Continues)

TABLE 2 | (Continued)

Study	Steatosis criteria	Cohort type	Cohort	Fibrosis stage	Outcome definition	Findings
Liu 2022 [42]	FLI ≥ 60	Community	*N* = 160,979, MASLD 100%, Age 58.0, Male 63.9%, White 100%, Black 0, Asian 0, Other 0, BMI: [< 25 (52.1), 25–29.9 (43.6), > 30 (4.2)], Follow-up: Median 8.2 years	Not available	ICD codes B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.0-K74.2, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4, I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7	GG vs. CC: HR 2.13 (1.85–2.46) CG vs. CC: HR 1.25 (1.16–1.34)
Mandorfer 2018 [16]	Steatosis based on transient elastography cutoffs	Medical centre	*N* = 141, MASLD 26.2%, ALD 73.8%, Age 58.6, Male 80%, Austrian: 100% (assumed), Follow-up: Median 27.4 months	All patients with portal hypertension (HVPG ≥ 6)	Requirement of paracentesis, admission for grade 3/4 HE, variceal bleeding and liver-related death	GG vs. non-GG: aSHR: 2.1 (1.1–4.0), $p = 0.024$
Miller 2023 [43]	Biopsy, VCTE-CAP > 250, or imaging	Medical centre	*N* = 31,505, MASLD 100%, Age: 50, Male 48.5% White 78.9%, Black 8%, Hispanic 4.3%, Asian 4.9%, Other 3.8%, BMI: 32.2, DM 28.0%, Follow-up: Median 4.6 years	4.3% patients with cirrhosis	ICD codes for ascites, variceal bleeding, HE, or HCC	No significant association; effect size not reported. Overlap with Wijarnpreecha 2023 and Chen 2023 (MGI).
Pennisi 2021 [44]	Ultrasound with 1 criterion of metabolic syndrome	Medical centre	*N* = 546, MASLD 100%, Age 50.8, Male 64.5%, Italian: 100% (assumed), BMI: 30.6, DM: 37.7%, Follow-up: Median 73.8 months	Not available	Liver decompensation (occurrence of ascites and/or bleeding varices and/or encephalopathy and/or jaundice) or HCC	Per G allele: Patients with FIB-4 > 1.3: HR 0.64 (0.18–2.28), $p = 0.49$
Rosso 2023 [45]	Biopsy	Hospital	*N* = 756, MASLD 100%, Age median 48, Male 64.7, BMI: 30, DM: 27.1, Follow-up: Median 84 months	Fibrosis stage on biopsy: 0 (25.5), 1 (30.6), 2 (21.3), 3 (15.3), 4 (7.3)	Liver decompensation, jaundice, variceal bleeding and encephalopathy	n (cumulative incidence rate per 1000 patient-years) CC: 12 (0.75), CG: 24 (1.03), GG: 12 (0.90), $p = 0.1651$
Seko 2023 [46]	Biopsy	Medical centre	*N* = 1550, MASLD 100%, Age median 59, Male 46.8%, Japanese: 100% (assumed), BMI: 27.4, DM: 58.4%, Follow-up: Median 7.1 years	Fibrosis stage on biopsy: 0 (442), 1 (489), 2 (271), 3 (277), 4 (71)	Composite endpoint of HCC, gastroesophageal varices/bleeding or decompensated cirrhosis	CG/GG vs. CC: HR 16.04 (2.24–115.04) $p = 0.017$

(Continues)

TABLE 2 | (Continued)

Study	Steatosis criteria	Cohort type	Cohort	Fibrosis stage	Outcome definition	Findings
Seko 2024 [47]	Biopsy	Medical centre	$N=1178$, MASLD 100%, Age 59.5, Male 47.5%, Japanese: 100% (assumed), BMI: 27.4, DM: 57.3%, Follow-up: Median 7.2 years	Fibrosis stage on biopsy: 0 (30.2), 1 (32.9), 2 (16.7), 3 (15.4), 4 (4.8)	Hospitalisation for any liver-related event, including HCC, GE varices, ascites and encephalopathy	CG vs. CC: HR 13.24 (95% CI, 1.80–97.24); $p=0.011$; GG vs. CC: 22.26 (95% CI, 3.07–161.46); $p=0.002$
Strebinger 2018 [48]	Clinical and histological diagnosis of MASLD	Medical centre	$N=254$, MASLD 100%, Age: 53, Male: 70.1%, Follow-up: 8.4 years	Not available	Incidence of hepatic events	GG vs. CC/CG: 8 (17.4%) vs. 18 (8.7%); $p=0.077$
Wijarnpreecha 2023 [49]	Imaging/Biopsy or VCTE	Medical centre	$N=13{,}420$, MASLD 100%, Age: 50.6, Male 47.2%, White 80.2%, Black 8.5%, Asian 4.9%, Other 6.4%, DM 22.7%, Follow-up: Median 49.3 months	Not available	Ascites, variceal bleeding, HE or HCC	GG vs. CC: Overall cohort: adjusted HR 1.87 (95% CI 1.04–3.34) $p=0.04$; CG vs. CC: Overall cohort: 1.05 (0.68–1.62) $p=0.81$. Overlap with Chen 2023 (MGI) and Miller 2023
HCC						
Grimaudo 2020 [38]	Biopsy or ultrasound with 1 criterion of metabolic syndrome	Medical centre	$N=471$, MASLD 100%, Age 49.4, Male 61.6%, Italian: 100% (assumed), BMI: 30.3, DM: 46.1%, Follow-up: Median 64.6 months	Fibrosis stage 3–4 on biopsy: 34.5%	HCC by imaging/histology	Per G allele: univariate: HR 2.26 (1.03–4.93) $p=0.04$; multivariate: HR 2.68 (1.01–7.26) $p=0.04$
Guyot 2013 [50]	Clinical discretion	Medical centre	$N=279$, ALD 100%, Age 56.7, Male 77.8%, French: 100% (assumed), White 100%, Black 0, Asian 0, Other 0, BMI: 27.4, DM 31.2%, Follow-up: 67 months	Not available	HCC by histology and arterial hypervascularization on imaging, or imaging with AFP ≥ 400	GG vs. CC: HR 1.9 (1.31–2.8) $p=0.0003$
Kawanaka 2022 [51]	Biopsy	Medical centre	$N=549$, MASLD 100%, Japanese: 100% (assumed), Follow-up: Median 6.5 years	Not available	HCC by imaging/histology	Cumulative incidence: CC: No cases CG: 3.9 per 1000 person-years GG: 8.3 per 1000 person-years (No HR given)

(Continues)

TABLE 2 | (Continued)

Study	Steatosis criteria	Cohort type	Cohort	Fibrosis stage	Outcome definition	Findings
Kogiso 2023 [52]	Biopsy/clinical guidelines	Medical centre	$N=402$, MASLD 84.3%, ALD 15.7%, Age 55, Male 56.7%, Japanese: 100% (assumed), BMI: 26.6, DM: 47.5%, Follow-up: 8.1 years	Fibrosis stage on biopsy: < F3: 193, ≥ F3: 111 (36.5%)	HCC by imaging/histology	Cumulative incidence: CC vs. GG/GC: 0% vs. 2.1% after 5 years ($p=0.17$)
Liu 2022 [42]	FLI ≥ 60	Community	$N=160{,}979$, MASLD 100%, Age 58.0, Male 63.9%, White 100%, Black 0, Asian 0, Other 0, BMI: [< 25 (52.1%), 25–29.9 (43.6%), > 30 (4.2%)], Follow-up: Median 8.2 years	Not available	ICD code for HCC	GG vs. CC: HR 2.85 (1.85–4.39) CG vs. CC: HR 1.12 (0.83–1.51)
Nahon 2024 [53]	Clinical discretion	Medical centre	$N=486$, ALD 100%, Age 58, Male 68.5, French: 100%, BMI: 27.5, DM: 22.7%, Follow-up: Median 43.7 months	All patients with cirrhosis	HCC by imaging/histology	CG or GG vs. CC: sHR = 1.52 (95% CI 0.85–2.73); $p=0.158$
Pelusi 2023 [54]	Clinical discretion	Medical centre	$N=449$, MASLD 100%, Age: 62, Male: 58%, BMI: 30, DM: 46%, Follow-up: Median 46 months	Mean FIB-4: 1.9; Mean LSM on Fibroscan: 13.3	HCC defined by imaging/ histology criteria	No significant association (effect size no reported). Possible overlap with Rosso 2023
Rosso 2023 [45]	Biopsy-proven	Medical centre	$N=756$, MASLD 100%, Age median 48, Male 64.7%, BMI: 30, DM: 27.1%, Follow-up: Median 84 months	Fibrosis stage on biopsy: 0 (25.5), 1 (30.6), 2 (21.3), 3 (15.3), 4 (7.3)	HCC defined by imaging/ histology criteria	*n* (cumulative incidence rate per 1000 patient-years) CC: 3 (0.19) vs. CG: 4 (0.65) vs. GG: 2 (0.15), $p=0.9551$
Seko 2023 [46]	Biopsy: steatosis in ≥ 5% of hepatocytes	Medical centre	$N=1550$, MASLD 100%, Age median 59, Male 46.8%, Japanese: 100% (assumed), BMI: 27.4, DM: 58.4%, Follow-up: Median 7.1 years	Fibrosis stage on biopsy: 0 (442), 1 (489), 2 (271), 3 (277), 4 (71)	HCC by imaging/histology	*n* (10-year incidence rate): GG: 40 (11.8%), CG: 31 (7.1%), CC: 0 ($p<0.05$); Cox proportional hazards analysis could not be performed due to no cases in the CC group
Thrift 2024 [55]	Imaging/Biopsy	Medical centre	$N=591$ (subset of cohort), MASLD 100%, Follow-up: Mean duration between enrollment and HCC development of 2.21 years	All patients with cirrhosis	HCC defined by histological or radiological diagnosis	CG/GG vs. CC: HR 1.68 (95% CI 0.65–4.33)

(Continues)

TABLE 2 | (Continued)

Study	Steatosis criteria	Cohort type	Cohort	Fibrosis stage	Outcome definition	Findings
Urias 2024 [56]	Imaging/Biopsy	Medical centre	$N=732$, ALD 18%, Non-viral non-alcohol-associated 56%, Age 57.6, Male 57.4%, White 91.1%, Black 3.9%, Hispanic 1.6%, Asian 3.3%, BMI: 30.9, DM 52.9%, Follow-up: Mean 6.6 years	All patients with cirrhosis	Liver Imaging Reporting and Data System-5 on imaging, or biopsy	5-year cumulative incidence: ALD: CC/CG vs. GG: 9.7% (5.2%–15.8%) vs. 17.1% (5.2%–35.0%), $p=0.044$ Non-viral nonalcohol-related liver disease 4.3% (2.3%–7.3%) versus 15.4% (7.5%–25.9%), $p=0.0001$
Liver-related mortality						
Grimaudo 2020 [38]	Biopsy or ultrasound with 1 criterion of metabolic syndrome	Medical centre	$N=471$, MASLD 100%, Age 49.4, Male 61.6%, Italian: 100% (assumed), BMI: 30.3, DM: 46.1%, Follow-up: Median 64.6 months	Fibrosis stage 3–4 on biopsy: 34.5%	Death recorded and classified according to liver-related events, including liver transplantation	Per G allele: univariate: HR, 2.42 (1.06–5.52) $p=0.03$; multivariate: HR 3.64 (1.18–11.2) $p=0.02$; Fine and Grey model for sub distribution hazard of hepatic mortality and considering hepatic mortality as a competing risk: sub-HR, 3.16 (1.26–9.89) $p=0.02$
Mandorfer 2018 [16]	Steatosis based on transient elastography cutoffs	Medical centre	$N=141$, MASLD 26.2%, ALD 73.8%, Age 58.6, Male 80%, Austrian: 100% (assumed), Follow-up: Median 27.4 months	All patients with portal hypertension (HVPG ≥ 6)	Liver-related mortality	GG vs. CG/CC: adjusted sHR: 2.2 (1.08–4.46) $p=0.029$
Meffert 2018 [57]	Ultrasound	Population	$N=4081$, German: 100% (assumed), Follow-up: Median 11.3 years	Not available	Cause of death based on ICD-10 codes	CG/GG vs. CC: HR 4.278 (1.170–15.640) $p=0.028$
Seko 2023 [46]	Biopsy	Medical centre	$N=1550$, MASLD 100%, Age median 59, Male 46.8%, Japanese: 100% (assumed), BMI: 27.4, DM: 58.4%, Follow-up: Median 7.1 years	Fibrosis stage on biopsy: 0 (442), 1 (489), 2 (271), 3 (277), 4 (71)	Death from HCC, variceal bleeding, or decompensated cirrhosis	Trend toward increased liver-related mortality by genotype ($p=0.053$); effect size not reported.

(Continues)

TABLE 2 | (Continued)

Study	Steatosis criteria	Cohort type	Cohort	Fibrosis stage	Outcome definition	Findings
Wijarnpreecha 2021 [58]	Ultrasound	Population	$N = 1952$, MASLD 100%, Follow-up: Median 20.1 years	Not available	ICD codes	GG vs. CC: age-and-sex-adjusted: 5.70 (1.23–26.46) $p = 0.028$; multivariable adjusted: HR 5.59 (1.08–28.79), $p = 0.041$ CG vs. CC: age-and-sex-adjusted: 3.82 (0.71–20.65) $p = 0.114$; multivariable adjusted: HR 3.55 (0.68–18.63), $p = 0.127$

Note: Unless otherwise specified, effect sizes are shown as subhazard ratio [sHR] or hazard ratio [HR] (95% confidence interval). GG, CG and CC refer to genotype of *PNPLA3*-rs738409.

Abbreviations: AFP, alpha fetoprotein; ALD, alcohol-associated liver disease; aSHR, adjusted subhazard ratio; BMI, body mass index; CAP, controlled attenuation parameter; CI, confidence interval; DM, diabetes mellitus; ESLD, end-stage liver disease; FIB-4, fibrosis-4 index; FLI, fatty liver index; GE, gastroesophageal; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; HVPG, hepatic venous pressure gradient; ICD, international classification of diseases; kPa, kilopascals; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; RRR, relative risk reduction; SBP, spontaneous bacterial peritonitis; VCTE, vibration-controlled transient elastography.

(Table 2). Of these studies, four studies [16, 38, 57, 58] reported that *PNPLA3*-rs738409-G allele was associated with increased risk (two comparing presence of G-allele, and two comparing GG vs. CC), and one study [46] with no difference. Among the three studies that could be included in the meta-analysis, pooled sHR was 2.83 (95% CI 1.58, 5.06) for rs738409-GG versus -CC (Figure 2B). An I^2 of 0% suggests that heterogeneity might not be important in this meta-analysis.

3.2.5 | Cardiovascular Disease

Seven studies with 19,371 participants assessed the association between *PNPLA3* and CVD incidence [12, 14, 15, 45, 46, 49, 59] (Table 3). Of these studies, one study [14] reported that the *PNPLA3*-rs738409-G allele was associated with increased risk (comparing GG vs. CC), and six studies [12, 15, 45, 46, 49, 59] showed no difference. Among the four studies that could be included in the meta-analysis, the pooled sHR for these studies showed no significant association with sHR 0.98 (95% CI 0.73, 1.32) for rs738409-GG versus -CC (Figure 2C). The meta-analysis had a low heterogeneity with I^2 of 28%.

3.2.6 | Cardiovascular Mortality

There were four studies with 8541 participants that assessed the association between *PNPLA3* and CVD-related mortality [46, 57, 62, 63] (Table 3). Of these studies, one study [46] reported that *PNPLA3*-rs738409-G allele was associated with increased risk, and three studies [57, 62, 63] reported no difference. Of the three studies in the meta-analysis, pooled sHR was 0.83 (95% CI 0.63, 1.1) for rs738409-GG versus -CC (Figure S2C). An I^2 of 0% suggests that heterogeneity might not be important in this meta-analysis.

3.2.7 | Extrahepatic Cancer

There were 10 studies with 25,735 participants that assessed the association between *PNPLA3* and extrahepatic cancer incidence [12, 14, 38, 41, 45, 46, 49, 57–59] (Table 3). Of these studies, one study [14] reported that the *PNPLA3*-rs738409-G allele was associated with increased risk (comparing GG vs. CC/CG), one study [41] reported a decreased risk (CG vs. CC), and eight studies [12, 38, 45, 46, 49, 57–59] found no difference. Of the five studies that could be included in the meta-analysis, the pooled sHR was 0.9 (95% CI 0.68, 1.18) for rs738409-GG versus -CC (Figure S2D). An I^2 of 0% suggests that heterogeneity might not be important in this meta-analysis.

3.2.8 | All-Cause Mortality

There were 15 studies with 28,854 participants that assessed the association between *PNPLA3* and all-cause mortality [12, 15, 16, 37, 41, 45, 46, 48, 49, 57, 62–66] (Table 3). Of these studies, five studies [16, 37, 48, 63, 64] reported that *PNPLA3*-rs738409-G allele was associated with increased risk (two studies comparing the presence of GG vs. CC, one comparing the presence of GG vs. CC/CG, one comparing the presence of CG/

Outcome	PNPLA3	TM6SF2	HSD17B13	MBOAT7	GCKR
Major adverse liver outcomes	15 4 0 N=270,833	5 3 0 N=211,197	0 5 1 N=10,201	1 3 0 N=169,636	0 2 0 N=8,110
Hepatocellular carcinoma	5 6 0 N=167,244	2 1 0 N=161,714	0 2 0 N=688	2 0 0 N=161,465	No studies
Cirrhosis	7 2 0 N=262,229	1 2 0 N=169,419	0 1 0 N=7,893	1 1 0 N=168,872	0 2 0 N=8,440
Liver-related mortality	4 1 0 N=8,195	0 1 0 N=443	0 1 0 N=202	No studies	No studies
Cardiovascular disease	1 6 0 N=19,371	0 1 0 N=547	1 0 0 N=165	0 1 0 N=547	0 1 0 N=547
Cardiovascular mortality	1 3 0 N=8,541	0 1 0 N=958	No studies	0 1 0 N=958	No studies
Extrahepatic cancer	1 8 1 N=25,735	0 1 0 N=407	0 1 0 N=407	No studies	No studies
Overall mortality	5 10 0 N=28,854	0 3 0 N=1,912	0 2 0 N=367	0 2 0 N=1,505	0 1 0 N=547

FIGURE 1 | Summary of gene variant effects on examined outcomes. Rows represent outcomes and columns represent genes with risk variants. *PNPLA3* refers to rs738409-G; *TM6SF2*, rs58542926-T; *HSD17B13*, rs72613567-TA or rs6834314-G; and *MBOAT7*, rs641738-T. Each cell depicts the number of studies showing that the variant is associated with increased risk (red), no difference (black) and decreased risk (blue), as well as the total number of patients in the cohorts assessing the outcome. *GCKR* outcomes are not shown due to lack of any associations.

GG vs. CC and one comparing per G-allele effect) and 10 studies [12, 15, 41, 45, 46, 49, 57, 62, 65, 66] with no difference. Of the nine studies that could be included in the meta-analysis, pooled HR for rs738409-GG versus -CC alleles was 1.24 (1.04, 1.47) (Figure 2D). An I^2 of 4.3% suggests that heterogeneity might not be important in this meta-analysis.

3.3 | TM6SF2-rs58542926

3.3.1 | Major Adverse Liver Outcomes

There were eight studies with 211,197 participants that assessed the association between *TM6SF2*-rs58542926-T (corresponding to p.Glu167Lys protein mutation) and MALO [15, 36, 40–42, 44, 47, 67] (Table 4) (Figure 1). Of these studies, five studies [36, 41, 42, 44, 47] reported that *TM6SF2*-rs58542926-T allele was associated with increased risk (four comparing CT/TT vs. CC, and one comparing both CT vs. CC and TT vs. CC) and three studies [15, 40, 67] with no difference. Of the four studies that could be included in the meta-analysis, the pooled sHR was not significant: sHR 1.78 (95% CI 0.93, 3.38) for rs58542926-CT/TT vs. CC (Figure 3A). The meta-analysis had a high heterogeneity with I^2 of 84.6%.

3.3.2 | Hepatocellular Carcinoma

Three studies with 161,714 participants assessed the association between *TM6SF2* and HCC [42, 53, 68] (Table 4). Of these studies, two studies [42, 68] reported that *TM6SF2*-rs58542926-T allele was associated with increased risk, and one study [53] with no difference. All three studies were included in the meta-analysis and pooled sHR was 2.12 (95% CI 1.66, 2.70) for rs58542926-CT/TT versus -CC (Figure 3B). An I^2 of 0% suggests that heterogeneity might not be important in this meta-analysis.

3.3.3 | Cirrhosis/Advanced Liver Disease

Three studies with 169,419 participants assessed the association between *TM6SF2*-rs58542926-T and cirrhosis/severe liver disease incidence [15, 36, 42] (Table S5). One study [42] reported that *TM6SF2*-rs58542926-T allele was associated with increased risk (comparing CT/TT vs. CC), and two studies [15, 36] reported no difference. Meta-analysis could not be performed because of insufficient studies reporting sHR.

3.3.4 | All-Cause Mortality

Three studies with 1912 participants in total assessed the association between *TM6SF2* and all-cause mortality [15, 41, 62] (Table S5). All three studies reported that the *TM6SF2*-rs58542926-T allele was associated with no difference in risk. Two studies were included in the meta-analysis, and the pooled sHR was 1.1 (95% CI 0.45, 2.73) for rs58542926-TT/CT versus -CC (Figure S3). The meta-analysis had a moderate heterogeneity with I^2 of 73%.

3.3.5 | Other Outcomes

There was no evidence of association between *TM6SF2* genotype and incidence of liver-related mortality (one study, 443 participants [67]) (Table 4), cardiovascular disease (one study, 547 participants [15]), cardiovascular mortality (one study, 958

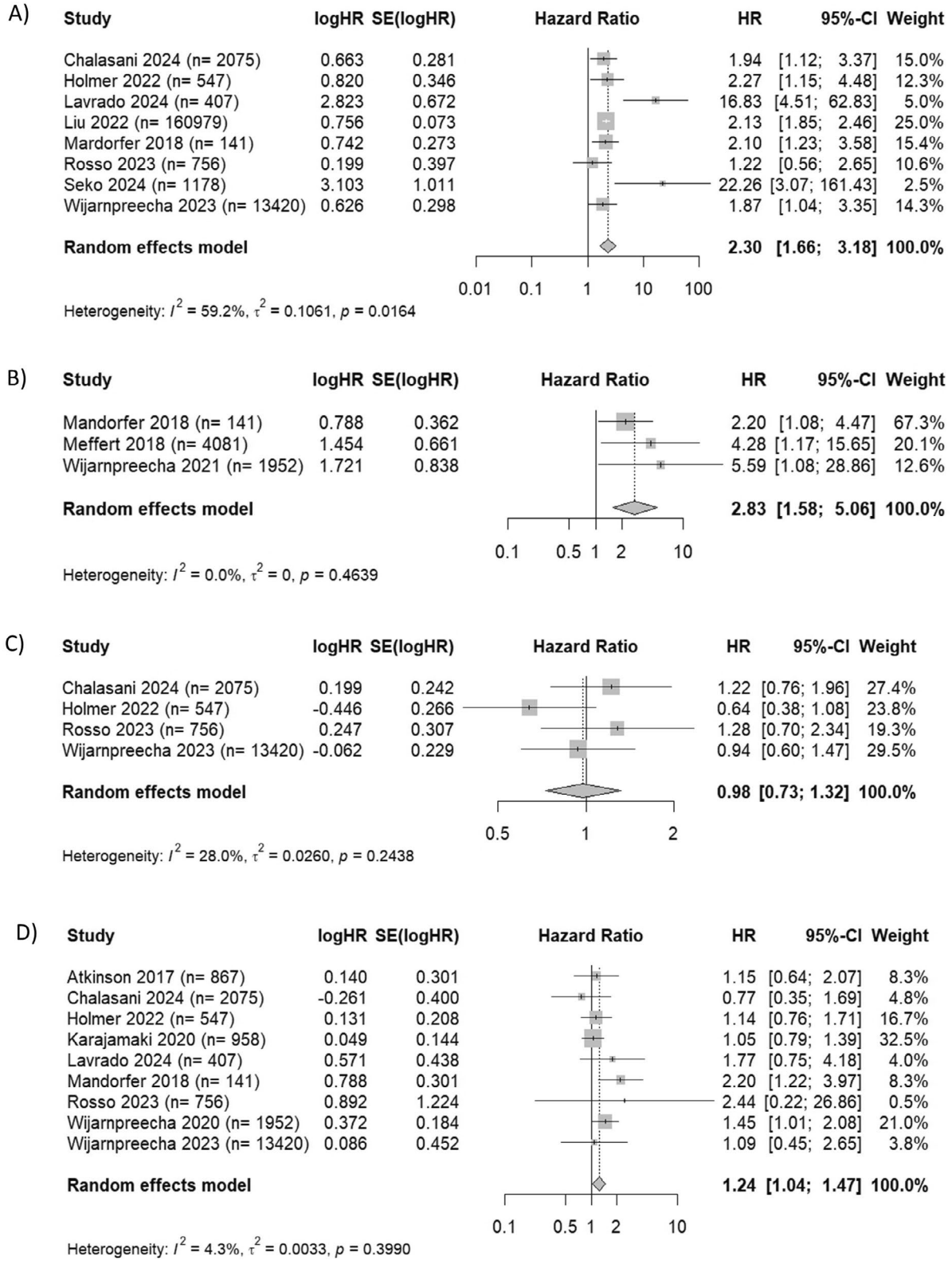

FIGURE 2 | Effect of *PNPLA3* genotype on clinical outcomes in patients with steatotic liver disease. Effect sizes are for *PNPLA3*-rs738409-GG versus CC genotype and are displayed as forest plots. (A) Major adverse liver outcomes (MALO). (B) Liver-related mortality. (C) Cardiovascular disease (CVD) incidence. (D) All-cause mortality.

TABLE 3 | *PNPLA3* non-liver related outcomes.

Study	Steatosis criteria	Cohort type	Cohort	Fibrosis stage	Outcome definition	Findings
CVD						
Akuta 2021 [14]	Biopsy	Medical centre	*N* = 477, MASLD 100%, Age 53, Male 59.1%, 100% Japanese, BMI 26.3, DM 32.7%, Follow-up: Median 5.9 years	Fibrosis stage (n): 0 (55), 1 (189), 2 (77), 3 (121), or 4 (35)	Heart failure, CAD, hypertension, orthostatic hypotension, shock, heart valve disease, endocarditis, arrhythmia, peripheral vascular disorders, diseases of the aorta and its branches, and stroke	CC vs. GG univariate: HR 2.97 (1.35–6.53) $p = 0.007$ Multivariate: HR 3.66 (1.61, 8.35) $p = 0.002$
Chalasani 2024 [12]	Biopsy	Medical centre	*N* = 2075, MASLD 100%, Age 50.4, Male 37.5%, White 74.8%, Black 3.0%, Hispanic 11.6%, Asian 6.0%, Other 4.5%, BMI: 34.4 DM 36.1%, Follow-up: Mean 4.3 years	Biopsy Fibrosis stages: 0: 25.1%, 1: 26.6%, 2: 18.8%, 3: 20.0%, 4: 9.5%	Death from heart or cerebrovascular events or the occurrence of new and nonfatal cardiovascular and cerebrovascular episodes (MI, unstable angina, heart failure and stroke)	Per G-risk allele: unadjusted HR 0.98 (0.77–1.24); Adj. sHR: 1.10 (0.86–1.40); CG vs. CC: unadjusted HR 0.94 (0.62–1.43); Adj. sHR: 1.04 (0.66–1.62); GG vs. CC: unadjusted HR 0.97 (0.60–1.55); Adj. sHR: 1.22 (0.76–1.96)
Holmer 2022 [15]	Imaging/biopsy	Medical centre	*N* = 547, MASLD 100%, Age median 51, Swedish: 100% (assumed), Male 62%, BMI 27.4, DM 19.1%, Follow-up: Median 19.6 years	Fibrosis stage %: 0 (24.6), 1 (38.7), 2 (22.2), 3 (10.3), 4 (4.2)	Acute ischemic heart disease or acute cerebrovascular disease using ICD codes	Unadjusted: CG vs. CC: 0.97 (0.71–1.31); GG vs. CC: 0.64 (0.39–1.05) Adjusted: CG vs. CC: HR 1.04 (0.76–1.44), GG vs. CC: HR 0.64 (0.38–1.08)
Rosso 2023 [45]	Biopsy	Medical centre	*N* = 756, MASLD 100%, Age median 48, Male 64.7%, BMI: 30, DM: 27.1%, Follow-up: Median 84 months	Fibrosis stage on biopsy: 0 (25.5), 1 (30.6), 2 (21.3), 3 (15.3), 4 (7.3)	NA	*n* (cumulative incidence rate per 1000 patient-years) CC: 19 (1.19) vs. CG: 28 (1.20) vs. GG: 20 (1.50), $p = 0.3992$

(Continues)

TABLE 3 | (Continued)

Study	Steatosis criteria	Cohort type	Cohort	Fibrosis stage	Outcome definition	Findings
Seko 2023 [46]	Biopsy: steatosis in ≥5% of hepatocytes	Medical centre	$N=1550$, MASLD 100%, Age median 59, Male 46.8%, Japanese: 100% (assumed), BMI: 27.4, DM: 58.4%, Follow-up: Median 7.1 years	Fibrosis stage on biopsy: 0 (442), 1 (489), 2 (271), 3 (277), 4 (71)	CAD, heart failure, or arrhythmia requiring hospitalisation	CG/GG vs. CC: HR 1.32 (0.63–2.80) $p=0.463$
Tai 2024 [59]	Ultrasound as well as CAP ≥222 dB/m or biopsy findings	Medical centre	$N=546$, MASLD 85.4%, ALD 14.6%, Age 54.7, Male 56%, Taiwanese: 100%, BMI: 27.38, Follow-up: 8 years	FIB-4: 1.18 ± 0.93	Ischemic heart disease, coronary revascularization, stroke, heart failure, cardiac arrest and cardiovascular death ICD-9 codes	Per G allele: HR 1.029 (0.861–1.23) $p=0.753$
Wijarnpreecha 2023 [49]	Imaging/Biopsy or VCTE	Medical centre	$N=13{,}420$, MASLD 100%, Age: 50.6, Male 47.2%, White 80.2%, Black 8.5%, Asian 4.9%, Other 6.4%, DM 22.7%, Follow-up: Median 49.3 months	Not available	ICD-10 codes: CAD I20–I25 Cerebrovascular accident I63–I66 Peripheral arterial disease I70–I72, I74–I75 Congestive heart failure I42–I43, I50	GG vs. CC: adjusted HR 0.94 (0.58–1.53) $p=0.81$; CG vs. CC: HR 1.06 (0.80–1.39) $p=0.69$
CVD-related mortality						
Käräjämäki 2020 [62]	Ultrasound	Community	$N=958$, MASLD 100%, Age 51.2, Male 47%, Finnish: 100% (assumed), BMI 27.7, DM 10%, Follow-up: Mean 21.0 years	Not available	CAD or stroke (subarachnoidal bleeding excluded) as a cause of death	CG/GG vs. CC: cumulative incidence 25/373 (7%) vs. 40/575 (7%) $p=0.944$
Meffert 2018 [57]	Ultrasound	Population	$N=4081$, German: 100% (assumed), Follow-up: Median 11.3 years	Not available	Cause of death based on ICD-10 codes	CG/GG vs. CC: HR: 0.670 (0.414–1.085) $p=0.103$

(Continues)

TABLE 3 | (Continued)

Study	Steatosis criteria	Cohort type	Cohort	Fibrosis stage	Outcome definition	Findings
Seko 2023 [46]	Biopsy: steatosis in ≥5% of hepatocytes	Medical centre	*N* = 1550, MASLD 100%, Age median 59, Male 46.8%, Japanese: 100% (assumed), BMI: 27.4, DM: 58.4%, Follow-up: Median 7.1 years	Fibrosis stage on biopsy: 0 (442), 1 (489), 2 (271), 3 (277), 4 (71)	Death from CVD (coronary vascular disease, heart failure, or arrhythmia requiring hospitalisation) or stroke (cerebral infarction, cerebral haemorrhage, or subarachnoid haemorrhage)	Higher risk of CVD-related mortality with GG genotype vs. CC ($p = 0.048$). No effect size given
Wijarnpreecha 2020 [63]	Ultrasound	Population	*N* = 1952, MASLD 100%, Age 43.4, Male 52.0%, BMI 28.6, DM 5.8% Non-Hispanic White 73%, Non-Hispanic Black 8.9%, Hispanic 8.3%, Other 9.8%, Follow-up: 20.06 years	Not available	NA	GG vs. CC: age, sex-adjusted: HR 0.81 (0.46–1.43) $p = 0.451$; Multivariable adjusted: HR 0.89 (95% CI 0.55–1.42), $p = 0.598$; CG vs. CC: age, sex-adjusted: HR 1.38 (0.93–2.04) $p = 0.107$; Multivariable adjusted: HR 1.28 (0.85–1.92), $p = 0.223$; *PNPLA3* as continuous: age, sex-adjusted: HR 1.10 (0.86–1.40) $p = 0.446$; Multivariable adjusted: HR 1.09 (0.88–1.35), $p = 0.412$
Extrahepatic malignancy						
Akuta 2021 [14]	Biopsy	Medical centre	*N* = 477, MASLD 100%, Age 53, Male 59.1%, 100% Japanese, BMI 26.3, DM 32.7%, Follow-up: Median 5.9 years	Fibrosis stage (n): 0 (55), 1 (189), 2 (77), 3 (121), or 4 (35)	Incidence of extrahepatic cancers	GG vs. CC/CG: univariate analysis: HR 3.64 (1.41–9.44) $p = 0.008$; not significant on multivariate analysis

(Continues)

TABLE 3 | (Continued)

Study	Steatosis criteria	Cohort type	Cohort	Fibrosis stage	Outcome definition	Findings
Chalasani 2024 [12]	Biopsy	Medical centre	$N = 2075$, MASLD 100%, Age 50.4, Male 37.5%, White 74.8%, Black 3.0%, Hispanic 11.6%, Asian 6.0%, Other 4.5%, BMI: 34.4 DM 36.1%, Follow-up: Mean 4.3 years	Biopsy Fibrosis stages: 0: 25.1%, 1: 26.6%, 2: 18.8%, 3: 20.0%, 4: 9.5%	Death from non-HCC cancers or new onset of non-HCC neoplasms	Per G allele: Adj. sHR: 1.02 (0.74–1.42) CG vs. CC: 1.01 (0.57–1.77) GG vs. CC: 1.05 (0.55–2.01)
Grimaudo 2020 [38]	Biopsy or ultrasound with 1 criterion of metabolic syndrome	Medical centre	$N = 471$, MASLD 100%, Age 49.4, Male 61.6%, Italian: 100% (assumed), BMI: 30.3, DM: 46.1%, Follow-up: Median 64.6 months	Fibrosis stage 3–4 on biopsy: 34.5%	Incidence of extrahepatic cancers	G allele not associated (no effect size given)
Lavrado 2024 [41]	Steatosis on ultrasonography	Medical centre	$N = 407$, MASLD 100%, Age 62.1, Male 32.4%, Brazilian: 100% (assumed), BMI: 31.5, DM 100%, Follow-up: Median 11 years	Elastography: Liver stiffness: 6.3 kPa; CAP: 291.6	Incidence of extrahepatic cancers (except skin cancer)	CG vs. CC: unadjusted: HR 0.43 (0.21–0.89) $p = 0.023$; multivariate: HR 0.40 (0.19–0.84) $p = 0.01$; GG vs. CC: unadjusted: HR 0.95 (0.36–2.47) $p = 0.91$; multivariate: HR 0.89 (0.33–2.42) $p = 0.82$
Meffert 2018 [16]	Ultrasound	Population	$N = 4081$, German: 100% (assumed), Follow-up: Median 11.3 years	Not available	Incidence of extrahepatic cancers	CG/GG vs. CC: HR 0.988 (0.635–1.538) $p = 0.946$
Rosso 2023 [45]	Biopsy-proven	Medical centre	$N = 756$, MASLD 100%, Age median 48, Male 64.7%, BMI: 30, DM: 27.1%, Follow-up: Median 84 months	Fibrosis stage on biopsy: 0 (25.5), 1 (30.6), 2 (21.3), 3 (15.3), 4 (7.3)	Incidence of extrahepatic cancers	*n* (cumulative incidence rate per 1000 patient-years) CC: 24 (1.57), CG: 21 (0.91), GG: 16 (1.21); CG/GG vs. CC: $p = 0.2800$
Seko 2023 [46]	Biopsy: steatosis in ≥ 5% of hepatocytes	Medical centre	$N = 1550$, MASLD 100%, Age median 59, Male 46.8%, Japanese: 100% (assumed), BMI: 27.4, DM: 58.4%, Follow-up: Median 7.1 years	Fibrosis stage on biopsy: 0 (442), 1 (489), 2 (271), 3 (277), 4 (71)	Incidence of extrahepatic cancers	CG/GG vs. CC: HR 1.19 (0.68–2.06) $p = 0.543$

(Continues)

TABLE 3 | (Continued)

Study	Steatosis criteria	Cohort type	Cohort	Fibrosis stage	Outcome definition	Findings
Tai 2024 [59]	Ultrasound as well as CAP ≥ 222 dB/m or biopsy findings	Medical centre	$N = 546$, MASLD 85.4%, ALD 14.6%, Age 54.7, Male 56%, Taiwanese: 100%, BMI: 27.38, Follow-up: 8 years	FIB-4: 1.18 ± 0.93	Incidence of extrahepatic cancers	Per G allele:: univariate: HR 0.682 (0.468–0.995) $p = 0.047$; multivariate: HR 0.638 (0.366–1.11) $p = 0.112$
Wijarnpreecha 2021 [58]	Ultrasound	Population	$N = 1952$, MASLD 100%, Follow-up: Median 20.1 years	Not available	ICD codes for extrahepatic cancer	GG vs. CC: HR 0.68 (0.28–1.65) $p = 0.373$; Per G allele: HR 1.07 (0.75–1.51) $p = 0.711$; CG/GG vs., CC:: HR 1.22 (0.76–1.95) $p = 0.390$
Wijarnpreecha 2023 [49]	Imaging/Biopsy or VCTE	Medical centre	$N = 13{,}420$, MASLD 100%, Age: 50.6, Male 47.2%, White 80.2%, Black 8.5%, Asian 4.9%, Other 6.4%, DM 22.7%, Follow-up: Median 49.3 months	Not available	Incidence of extrahepatic cancers	CG vs. CC: 0.90 (0.70–1.14) $p = 0.38$; GG vs. CC: 0.93 (0.62–1.39) $p = 0.73$
All-cause mortality						
Atkinson 2017 [64]	Clinical/lab features of alcohol-associated hepatitis, DF ≥ 32	Medical centre	$N = 867$, ALD 100%, Age 48.8, Male 63.8%, British 100%, White: 95.8%, Black: 0.3%, Asian: 2.6%, Other: 1.4%, Follow-up: Median 844 days	Not available	Mortality endpoints	No effect on 28- or 90-day survival. In patients surviving beyond 90 days, GG was associated with a significant increase in mortality at day 450: cumulative incidence GG: 34.7% (17/49); CG: 21.8% (53/243); CC: 25.1% (74/295); $p = 0.04$
Chalasani 2024 [12]	Biopsy	Medical centre	$N = 2075$, MASLD 100%, Age 50.4, Male 37.5%, White 74.8%, Black 3.0%, Hispanic 11.6%, Asian 6.0%, Other 4.5%, BMI: 34.4 DM 36.1%, Follow-up: Mean 4.3 years	Biopsy Fibrosis stages: 0: 25.1%, 1: 26.6%, 2: 18.8%, 3: 20.0%, 4: 9.5%	Any cause of death	Per G allele: unadjusted HR 0.78 (0.54–1.13), sHR 0.86 (0.57–1.27); CG vs. CC: unadjusted HR 0.76 (0.41–1.40), sHR 0.72 (0.38–1.38); GG vs. CC: unadjusted HR 0.61 (0.29–1.29), sHR 0.77 (0.35–1.67)

(Continues)

TABLE 3 | (Continued)

Study	Steatosis criteria	Cohort type	Cohort	Fibrosis stage	Outcome definition	Findings
Friedrich 2014 [37]	Clinical discretion	Medical centre	*N* = 105, ALD 100%, Age: 52.6, Male: 74.3%, White: 100%, BMI: 26.7, Follow-up: NA	All patients with ESLD	Overall survival free of liver transplantation	Overall survival: CC = 30.7 ± 7.9 months; CG/GG: 17.1 ± 3.3 months; $p = 0.012$
Holmer 2022 [15]	Imaging/biopsy	Medical centre	*N* = 547, MASLD 100%, Age median 51, Swedish: 100% (assumed), Male 62%, BMI 27.4, DM 19.1%, Follow-up: Median 19.6 years	Fibrosis stage %: 0 (24.6), 1 (38.7), 2 (22.2), 3 (10.3), 4 (4.2)	ICD-8, ICD-9 and ICD-10 codes used to define cause of death	Unadjusted: CG vs. CC: HR 1.03 (0.79–1.36), GG vs. CC: HR 1.03 (0.69–1.53) Adjusted: CG vs. CC: HR 0.93 (0.69–1.25), GG vs. CC: HR 1.14 (0.76–1.73)
Käräjämäki 2020 [62]	Ultrasound	Community	*N* = 958, MASLD 100%, Age 51.2, Male 47%, Finnish: 100% (assumed), BMI 27.7, DM 10%, Follow-up: Mean 21.0 years	Not available	ICD-8, ICD-9 and ICD-10 codes used to define cause of death	CG/GG vs. CC: HR 1.050 (95% CI: 0.792–1.391) $p = 0.736$
Kogiso 2021 [65]	Biopsy/clinical guidelines	Medical centre	*N* = 314, MASLD 100%, Age 53, Male 51.3%, Japanese: 100% (assumed), BMI: 27.1, DM: 49.4%, Follow-up: Median 7 years	Fibrosis stage on biopsy: F0-F2: 190 (62.5%), ≥ F3: 111 (37.5%); Mean FIB-4: 1.38	Any cause of death	GG vs. CG/CC: No significant association ($p = 0.34$), no effect size given
Lavrado 2024 [41]	Steatosis on ultrasonography	Medical centre	*N* = 407, MASLD 100%, Age 62.1, Male 32.4%, Brazilian: 100% (assumed), BMI: 31.5, DM 100%, Follow-up: Median 11 years	Elastography: Liver stiffness: 6.3 kPa; CAP: 291.6	Overall mortality	CG vs. CC: Crude/unadjusted: HR 0.91 (0.50–1.63) $p = 0.74$; age, sex-adjusted: HR 0.89 (0.49–1.61) $p = 0.69$; multivariable adjusted: HR 0.89 (0.48–1.65) $p = 0.71$ GG vs. CC: Crude/unadjusted: HR 1.64 (0.75–3.58) $p = 0.22$; age, sex-adjusted: HR 1.85 (0.85–4.03) $p = 0.12$; multivariable adjusted: HR 1.77 (0.75–4.20) $p = 0.19$

(Continues)

TABLE 3 | (Continued)

Study	Steatosis criteria	Cohort type	Cohort	Fibrosis stage	Outcome definition	Findings
Mandorfer 2018 [16]	Steatosis based on transient elastography cutoffs	Medical centre	$N=141$, MASLD 26.2%, ALD 73.8%, Age 58.6, Male 80%, Austrian: 100% (assumed), Follow-up: Median 27.4 months	All patients with portal hypertension (HVPG ≥ 6)	Any cause of death	GG vs. non-GG: aSHR: 2.2 (1.22–3.98, $p=0.009$)
Meffert 2018 [57]	Ultrasound	Population	$N=4081$, German: 100% (assumed), Follow-up: Median 11.3 years	Not available	ICD-10 codes	CG/GG vs. CC: HR 0.892 (0.749–1.063) $p=0.202$
Rosso 2023 [45]	Biopsy	Medical centre	$N=756$, MASLD 100%, Age median 48, Male 64.7%, BMI: 30, DM: 27.1%, Follow-up: Median 84 months	Fibrosis stage on biopsy: 0 (25.5), 1 (30.6), 2 (21.3), 3 (15.3), 4 (7.3)	Any cause of death	*n* (cumulative incidence rate per 1000 patient-years) CC: 1 (0.05) vs. CG: 6 (0.26) vs. GG: 2 (0.15) $p=0.1491$
Seko 2023 [46]	Biopsy: steatosis in ≥ 5% of hepatocytes	Medical centre	$N=1550$, MASLD 100%, Age median 59, Male 46.8%, Japanese: 100% (assumed), BMI: 27.4, DM: 58.4%, Follow-up: Median 7.1 years	Fibrosis stage on biopsy: 0 (442), 1 (489), 2 (271), 3 (277), 4 (71)	Any cause of death	CG/GG vs. CC: HR 1.50 (0.60–3.78) $p=0.387$
Strebinger 2018 [48]	Clinical and histological diagnosis of MASLD	Medical centre	$N=254$, MASLD 100%, Age: 53, Male: 70.1%, Follow-up: 8.4 years	Not available	Death of any cause or liver transplantation	Significantly decreased overall survival in GG vs. CC ($p=0.033$) and CC/CG patients combined ($p=0.021$); effect size not reported
Wijarnpreecha 2020 [63]	Ultrasound	Population	$N=1952$, MASLD 100%, Age 43.4, Male 52.0%, BMI 28.6, DM 5.8% Non-Hispanic White 73%, Non-Hispanic Black 8.9%, Hispanic 8.3%, Other 9.8%, Follow-up: 20.06 years	Not available	Any cause of death	CG vs. CC: age, sex-adjusted: 1.22 (0.97–1.54) $p=0.088$; multivariable adjusted: HR 1.18 (0.94–1.47), $p=0.148$ GG vs. CC: age, sex-adjusted: 1.22 (0.79–1.90) $p=0.349$; multivariable adjusted: HR 1.45, (1.01–2.08), $p=0.047$ Per G allele as continuous: age, sex-adjusted: 1.15 (0.95–1.40) $p=0.151$; multivariable adjusted: HR 1.19 (1.02–1.39), $p=0.025$

(Continues)

TABLE 3 | (Continued)

Study	Steatosis criteria	Cohort type	Cohort	Fibrosis stage	Outcome definition	Findings
Wijarnpreecha 2023 [49]	Imaging/Biopsy or VCTE	Medical centre	$N = 13,420$, MASLD 100%, Age: 50.6, Male 47.2%, White 80.2%, Black 8.5%, Asian 4.9%, Other 6.4%, DM 22.7%, Follow-up: Median 49.3 months	Not available	Any cause of death	CG vs. CC: HR 0.97 (0.56–1.68) $p = 0.90$ GG vs. CC: HR 1.09 (0.45–2.66) $p = 0.85$
Younes 2022 [66]	Biopsy	Medical centre	$N = 1339$, MASLD 100%, Age: 48, Male: 64.5%, BMI: 29.8, DM: 28.2%, Follow-up: Median 94 months	Fibrosis stages: 0 (26.8%), 1–2 (50.3%), 3–4 (22.8%)	Any cause of death	GG vs. CC/CG: HR 1.4 (0.26–7.54) $p = 0.69$ after adjustment for BMI, age, sex fibrosis stage and diabetes.

Note: Unless otherwise specified, effect sizes are shown as subhazard ratio [sHR] or hazard ratio [HR] (95% confidence interval). GG, CG and CC refer to genotype of *PNPLA3*-rs738409.
Abbreviations: ALD, alcohol-associated liver disease; aSHR, adjusted subhazard ratio; BMI, body mass index; CAD, coronary artery disease; CAP, controlled attenuation parameter; CI, confidence interval; DM, diabetes mellitus; ESLD, end-stage liver disease; FIB-4, fibrosis-4 index; ICD, international classification of diseases; kPa, kilopascals; MASLD, metabolic dysfunction-associated steatotic liver disease; MI, myocardial infarction; VCTE, vibration-controlled transient elastography.

participants [62]), or extrahepatic cancer (one study, 407 participants [41]) (Table S5).

3.4 | *HSD17B13*-rs72613567 or rs6834314

3.4.1 | Major Adverse Liver Outcomes

There were six studies with 10,201 participants that assessed the association between *HSD17B13* rs72613567 or rs6834314 and MALO [36, 40, 44, 47, 69, 70] (Table S6) (Figure 1). Of these studies, five studies [36, 40, 44, 47, 69] reported that the *HSD17B13* rs72613567 splice variant (previously reported as protective) was associated with no difference in risk, and one study [70] reported a decreased risk on multivariable regression (comparing rs72613567 TA/TA vs. AA) though this model was unstable. Of the two studies that could be included in the meta-analysis, the pooled sHR for these studies was not significant: sHR 0.96 (95% CI 0.63, 1.46) when comparing rs72613567-TA/TA, T/TA versus -T/T (Figure S4). The meta-analysis had a low heterogeneity with I^2 of 44.7%.

3.4.2 | Other Outcomes

There was no evidence of association between *HSD17B13* genotype and incidence of HCC (two studies, 688 participants [53, 69]), cirrhosis/advanced liver disease (one study, 7893 participants [36]), liver-related mortality (one study, 202 participants [69]), cardiovascular disease (one study, 165 participants [70]), extrahepatic cancer (one study, 407 participants [70]), or all-cause mortality (two studies, 367 participants) [69, 70] (Table S6). Meta-analysis was not possible for any of these outcomes due to differences in effect reporting.

3.5 | *MBOAT7*-rs641738

3.5.1 | Major Adverse Liver Outcomes

There were four studies with 169,636 participants that assessed the association between *MBOAT7*-rs641738 and MALO [15, 36, 40, 42] (Table S7) (Figure 1). Of these studies, one study [42] reported that *MBOAT7* risk allele was associated with increased risk, and three studies [15, 36, 40] with no difference. Of the three studies that could be included in the meta-analysis, the pooled sHR for these studies was significant: sHR 1.21 (95% CI 1.1, 1.33) for rs641738-TT versus -CC (Figure S5A). An I^2 of 0% suggests that heterogeneity might not be important in this meta-analysis.

3.5.2 | Hepatocellular Carcinoma

There were two studies with 161,465 participants that assessed the association between *MBOAT7*-rs641738 and HCC incidence [42, 53] (Table S7). Of these studies, both studies reported that *MBOAT7* risk allele was not associated with increased risk. Both studies were included in the meta-analysis; pooled sHR for these studies was 1.43 (95% CI 1.04, 1.99) for rs641738-TT versus -CC (Figure S5B). An I^2 of 0% suggests that heterogeneity might not be important in this meta-analysis.

TABLE 4 | *TM6SF2* outcomes.

Study	Steatosis criteria	Cohort type	Cohort	Fibrosis stage	Outcome definition	Findings
MALO						
Balcar 2023 [67]	LSM ≥ 10 kPa and/or an HVPG ≥ 6 mmHg	Medical centre	*N* = 443, MASLD 22.8%, ALD 77.2%, 91% European, 7% Arabic, 1.4% Asian, 0.3% African, Follow-up: Median 70.8 months	Not available	Cumulative incidence of hepatic decompensation/liver transplantation/ liver-related death; Hepatic decompensation defined by the presence/history of at least one decompensating event, that is, ascites, variceal bleeding, or HE	CT/TT vs. CC: HR 1.08 (0.80–1.44) $p = 0.62$
Chen 2022 (UKBB) [36]	Labs or ICD code	Community	*N* = 46,880, MASLD 100%, Age 55.6, Male 52.0% White 93.9%, Black 1.3%, Asian 2.6%, Other 2.2% BMI: lean 23.3, overweight 40.5, obese class I 31.6, obese class II 10.6, obese class III 4.0 DM 9.7%, Follow-up: Median 106.3 months	FIB-4: < 1.3 (45.3), 1.3–2.67 (50.8), > 2.67 (3.8)	ICD codes for cirrhosis or portal hypertensive complications	CT vs. CC: HR 1.52 (1.13–2.05) $p = 0.0054$ TT vs. CC: HR 3.14 (1.39–7.13) $p = 0.0061$
Holmer 2022 [15]	Imaging/biopsy	Medical centre	*N* = 547, MASLD 100%, Age median 51, Swedish: 100% (assumed), Male 62%, BMI 27.4, DM 19.1%, Follow-up: Median 19.6 years	Fibrosis stage %: 0 (24.6), 1 (38.7), 2 (22.2), 3 (10.3), 4 (4.2)	ICD codes; severe liver disease defined as cirrhosis, decompensation with ascites, EV, HE, portal hypertension, HRS, HCC	Unadjusted: CT vs. CC: 0.90 (0.51–1.60), TT vs. CC: 0.93 (0.29–2.98) Adjusted: CT vs. CC: HR 0.85 (0.44–1.63), TT vs. CC: HR 1.06 (0.26–4.45)
Kocas-Kilicarslan 2024 [40]	Imaging	Medical centre	*N* = 217, MASLD 100%, Age 54.7, Male 36.4%, White: 61.7% African American: 2.7%, Hispanic: 0%, Asian: 1.5%, Other: 0.9%, No data: 69.44%, BMI: 34.0, DM: 42.9%, Follow-up: NA	Not available	Progression to ESLD	CT/TT vs. CC: RRR 0.658 (0.294–1.475) $p = 0.310$
Lavrado 2024 [41]	Steatosis on ultrasonography	Medical centre	*N* = 407, MASLD 100%, Age 62.1, Male 32.4%, Brazilian: 100% (assumed), BMI: 31.5, DM 100%, Follow-up: Median 11 years	Elastography: Liver stiffness: 6.3 kPa; CAP: 291.6	Cirrhosis complications registered were HCC and oesophageal/gastric varices, with or without previous bleeding	CT/TT: vs. CC crude: HR 7.86 (3.14–19.67) $p < 0.001$; age, sex-adj: HR 7.26 (2.86–18.38) $p < 0.001$; multi adj: HR 6.62 (2.41–18.20) $p < 0.001$

(Continues)

TABLE 4 | (Continued)

Study	Steatosis criteria	Cohort type	Cohort	Fibrosis stage	Outcome definition	Findings
Liu 2022 [42]	FLI ≥ 60	Community	*N* = 160,979, MASLD 100%, Age 58.0, Male 63.9%, White 100%, Black 0, Asian 0, Other 0, BMI: [< 25 (52.1), 25–29.9 (43.6), > 30 (4.2)], Follow-up: Median 8.2 years	Not available	ICD codes B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.0-K74.2, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4, I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7	CT/TT vs. CC: HR 1.26 (1.14–1.39)
Pennisi 2021 [44]	Ultrasound with one criterion of metabolic syndrome	Medical centre	*N* = 546, MASLD 100%, Age 50.8, Male 64.5%, Italian: 100% (assumed), BMI: 30.6, DM: 37.7%, Follow-up: Median 73.8 months	Not available	Liver decompensation (occurrence of ascites and/or bleeding varices and/or encephalopathy and/or jaundice) or HCC	Patients with FIB-4 ≥ 1.3: CT/TT vs. CC: HR 1.94 (1.00–3.77) $p = 0.04$
Seko 2024 [47]	Biopsy	Medical centre	*N* = 1178, MASLD 100%, Age 59.5, Male 47.5%, Japanese: 100% (assumed), BMI: 27.4, DM: 57.3%, Follow-up: Median 7.2 years	Fibrosis stage on biopsy: 0 (30.2), 1 (32.9), 2 (16.7), 3 (15.4), 4 (4.8)	Hospitalisation for any liver-related event, including HCC, GE varices, ascites and encephalopathy	CT/TT vs. CC: HR 2.42 (1.50–3.90) $p < 0.01$
HCC						
Liu 2022 [42]	FLI ≥ 60	Community	*N* = 160,979, MASLD 100%, Age 58.0, Male 63.9%, White 100%, Black 0, Asian 0, Other 0, BMI: [< 25 (52.1), 25–29.9 (43.6), > 30 (4.2)], Follow-up: Median 8.2 years	Not available	ICD code for HCC	CT/TT vs. CC: HR 2.12 (1.57–2.86)
Nahon 2015 [68]	Clinical discretion	Medical centre	*N* = 249 (subset of larger cohort), ALD 100%, French: 100%, Follow-up: 68 months	All patients with cirrhosis	NA	CT/TT vs. CC: HR = 2.49 (1.5–4.5) $p = 0.003$
Nahon 2024 [53]	Clinical discretion	Medical centre	*N* = 486, ALD 100%, Age 58, Male 68.5, French: 100%, BMI: 27.5, DM: 22.7%, Follow-up: Median 43.7 months	All patients with cirrhosis	HCC by imaging/histology	CT or TT vs. CC: SHR = 1.66; (0.86–3.19); $p = 0.129$
Liver-related mortality						
Balcar 2023 [67]	LSM ≥ 10 kPa and/or an HVPG ≥ 6 mmHg	Medical centre	*N* = 443, MASLD 22.8%, ALD 77.2%, 91% European, 7% Arabic, 1.4% Asian, 0.3% African, Follow-up: Median 70.8 months	Not available	Cumulative incidence of requirement of liver transplantation/liver-related death	CT/TT vs. CC: HR 0.90 (0.59–1.37) $p = 0.62$

Note: Unless otherwise specified, effect sizes are shown as subhazard ratio [sHR] or hazard ratio [HR] (95% confidence interval). TT, CT and CC refer to genotype of *TM6SF2*-rs58542926.
Abbreviations: ALD, alcohol-associated liver disease; BMI, body mass index; CAP, controlled attenuation parameter; DM, diabetes mellitus; ESLD, end-stage liver disease; EV, oesophageal varices; FIB-4, fibrosis-4 index; FLI, fatty liver index; GE, gastroesophageal; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; HVPG, hepatic venous pressure gradient; ICD, international classification of diseases; kPa, kilopascals; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; VCTE, vibration-controlled transient elastography.

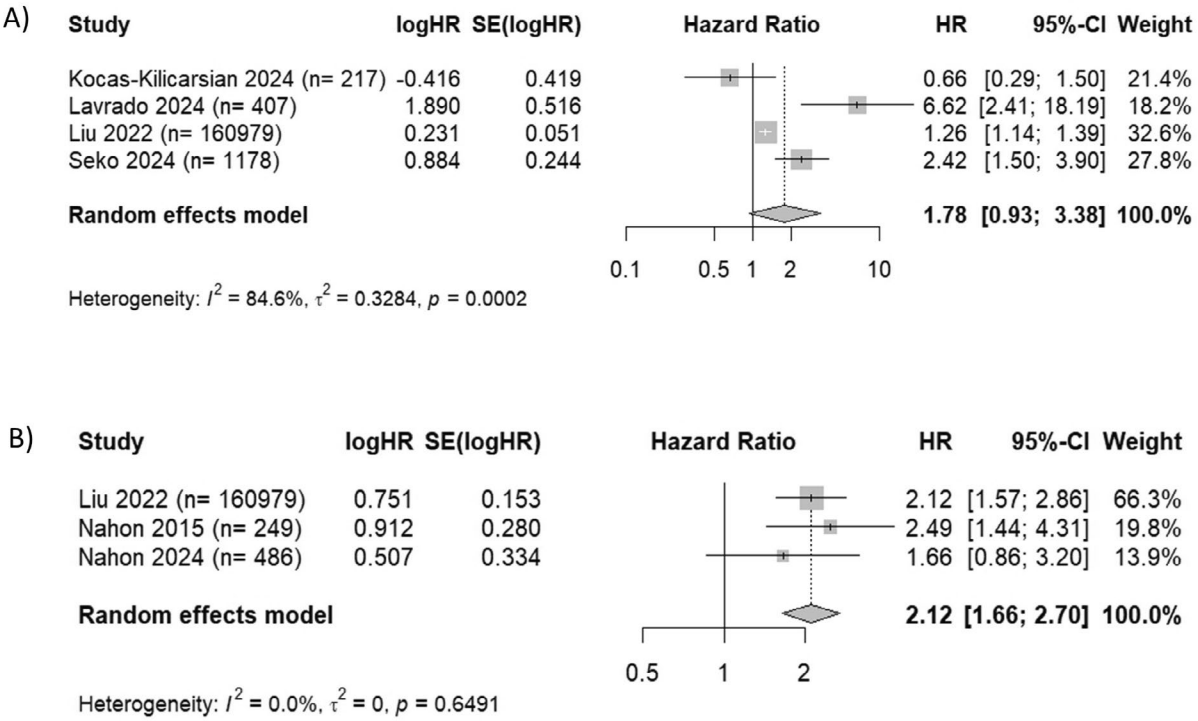

FIGURE 3 | Effect of *TM6SF2* genotype on clinical outcomes in patients with steatotic liver disease. Effect sizes are for *TM6SF2*-rs58542926-TT/CT versus CC genotype and are displayed as forest plots. (A) Major adverse liver outcomes (MALO). (B) Hepatocellular carcinoma (HCC) incidence.

3.5.3 | Cirrhosis/Advanced Liver Disease

Two studies with 168,872 participants assessed the association between *MBOAT7*-rs641738 and cirrhosis incidence [36, 42] (Table S7). Of these studies, one study [42] reported that the *MBOAT7* risk allele was associated with increased risk (comparing rs641738-CT vs. rs641738-CC), and one study [36] with no difference. Of the two studies that could be included in the meta-analysis, the pooled sHR for these studies was significant: sHR 1.49 (95% CI 1.14, 1.94) for rs641738-TT versus -CC (Figure S5C). The meta-analysis had a low heterogeneity with I^2 of 27.3%.

3.5.4 | All-Cause Mortality

Two studies with 1505 participants assessed the association between *MBOAT7*-rs641738 and all-cause mortality [15, 62] (Table S7). Both were included in the meta-analysis and the pooled sHR for these studies was 0.78 (95% CI 0.62, 0.98) for rs641738-TT versus -CC (Figure S5D). An I^2 of 0% suggests that heterogeneity might not be important in this meta-analysis.

3.5.5 | Cardiovascular Disease/Death

There was no evidence of association between *MBOAT7* genotype and cardiovascular disease (one study, 547 participants [15]) or death (one study, 958 participants [62]) (Table S7).

3.6 | GCKR

There was no evidence of association between *GCKR*-rs1260326 genotype and MALO (two studies, 8110 participants [36, 40]), cirrhosis/advanced liver disease (two studies, 8440 participants [15, 36]), CVD (one study, 547 participants [15]), or all-cause mortality (one study, 547 participants [15]) (Table S8) (Figure 1). Meta-analysis was not possible for any of these outcomes due to differences in effect reporting.

3.7 | Subgroup Analyses: Fibrosis

3.7.1 | Histologic Fibrosis

There were five studies with 5535 participants that compared outcomes by the level of baseline histologic fibrosis [12, 15, 35, 38, 45] (Table 5). All five examined *PNPLA3* rs738409-G genotype as a predictor. Two studies [12, 15] ($n = 2622$) showed that the *PNPLA3* gene variant significantly increased the risk of MALO in F0-F2 (sHR ranging from 2.49 to 2.76); one did not report an effect in F0-2, but it was likely not significant on inspection [45]; one did not include F0–2 patients [38]; and one included F0-1 but did not report effect size/significance [35]. Three studies [12, 35, 38] ($n = 4232$) reported that *PNPLA3* G allele was significant in F3-F4 (sHR ranging from 2.00 to 18.19) and two [15, 45] found that it was not. One study [12] ($n = 2075$) directly compared effect size in F0-F2 versus F3-F4 and found that it was greater in F3-F4, whereas one study [15] ($n = 547$) found that it was greater in F0-F2. Grimaudo et al. also reported that those with the *PNPLA3* variant and F3-F4 fibrosis had a significantly increased risk of HCC (sHR 2.66 [95% CI 1.02–7.13] $p = 0.04$) and liver-related mortality (sHR 3.64 [95% CI 1.18–11.2] $p = 0.02$) [38]. Kogiso et al. reported a higher incidence of HCC in *HSD17B13* rs72613567-A/A than other genotypes among those with FIB-4 < 2.67 ($p = 0.04$), but not FIB-4 ≥ 2.67 [52].

TABLE 5 | Outcomes by fibrosis stage.

Study	Cohort	Fibrosis measurement	Findings
PNPLA3: MALO			
Combination of cirrhosis and no cirrhosis			
Armisen 2023 [35]	$N = 1686$, MASLD 100%, Age: 48, Male 29%, Hispanic/Latino 2%, BMI: 42.3, DM 39%, Follow-up: NA	Histologic F0-F1 vs. F2-F4	G allele was associated with MALO in both groups after adjustment for fibrosis stage
Chalasani 2024 [12]	$N = 2075$, MASLD 100%, Age 50.4, Male 37.5%, White 74.8%, Black 3.0%, Hispanic 11.6%, Asian 6.0%, Other 4.5%, BMI: 34.4 DM 36.1%, Follow-up: Mean 4.3 years	Histologic F0-F2 vs. F3-F4	Referent: *PNPLA3* CC genotype without AF No AF and CG/GG: Adj. sHR: 2.76, 95% CI: 1.00–9.49 AF and CC: Adj. sHR: 14.76, 95% CI: 4.21–51.55 AF and CG/GG: Adj. sHR: 18.19, 95% CI: 5.60–59.20
Chen 2022 (MGI) [36]	$N = 7893$, MASLD 100%, Age 52.3, Male 43.1%, White 85.8%, Black 5.8%, Asian 3.1%, Other 2.2%, BMI: lean 15.4, overweight 26.6, obese class I 26.5, obese class II 16.5, obese class III 14.9 DM 35.5%, Follow-up: Median 71.6 months	FIB-4 < 1.3, 1.3–2.67, vs. > 2.67	*PNPLA3* CG vs. CC: no difference in any FIB-4 category. GG vs. CC: risk was significantly higher in all FIB-4 categories. FIB-4 < 1.3: sHR 2.99 (95% CI 1.38–6.45) $p = 0.0053$; FIB-4 1.3–2.67: sHR 3.07 (95% CI 1.66–5.66) $p = 0.00033$; FIB-4 > 2.67: sHR 3.77 (95% CI 1.47–9.68) $p = 0.0058$
Chen 2022 (UKBB) [36]	$N = 46{,}880$, MASLD 100%, Age 55.6, Male 52.0% White 93.9%, Black 1.3%, Asian 2.6%, Other 2.2% BMI: lean 23.3, overweight 40.5, obese class I 31.6, obese class II 10.6, obese class III 4.0 DM 9.7%, Follow-up: Median 106.3 months	FIB-4 < 1.3, 1.3–2.67, vs. > 2.67	*PNPLA3* CG vs. CC: no difference in any FIB-4 category. GG vs. CC: risk was significantly higher only in FIB-4 > 2.67: sHR 2.17 (1.26–3.71) $p = 0.0049$
Grimaudo 2020 [38]	$N = 471$, MASLD 100%, Age 49.4, Male 61.6%, Italian: 100% (assumed), BMI: 30.3, DM: 46.1%, Follow-up: Median 64.6 months	Histologic F3-F4	CG/GG vs. CC: HR 2.00 (1.01–3.97) $p = 0.04$
Holmer 2022 [15]	$N = 547$, MASLD 100%, Age median 51, Swedish: 100% (assumed), Male 62%, BMI 27.4, DM 19.1%, Follow-up: Median 19.6 years	Histologic F0-F2 or VCTE LSM < 15 kPa, vs. histologic F3-F4 or VCTE LSM ≥ 15 kPa	GG vs. CC: higher risk in non-advanced disease (aHR 2.49, 95% CI = 1.05–5.89). No difference in the group with advanced fibrosis (aHR 0.89, 95% CI = 0.21–3.74)
Pennisi 2021 [44]	$N = 546$, MASLD 100%, Age 50.8, Male 64.5%, Italian: 100% (assumed), BMI: 30.6, DM: 37.7%, Follow-up: Median 73.8 months	FIB-4 ≥ 1.3	No significant association between PNPLA3 genotype and MALO in FIB-4 ≥ 1.3: PNPLA3 rs738409: HR 0.64 (0.18–2.28) $p = 0.49$. Results were not reported for FIB-4 < 1.3.

(Continues)

TABLE 5 | (Continued)

Study	Cohort	Fibrosis measurement	Findings
Rosso 2023 [45]	*N* = 756, MASLD 100%, Age median 48, Male 64.7%, BMI: 30, DM: 27.1%, Follow-up: Median 84 months	Histologic F0-F2 vs. histologic F3-F4	CG/GG vs. CC: no difference in F3-4 cohort: incidence 18.5% vs. 19.6%, respectively ($p = 0.871$). Incidence of MALO by *PNPLA3* genotype in F0-2 was not reported but likely not significant based on the figure
Cirrhosis-only cohorts			
Friedrich 2014 [37]	*N* = 105, ALD 100%, Age: 52.6, Male: 74.3%, White: 100%, BMI: 26.7, Follow-up: NA	All patients with ESLD	Time to decompensation: *PNPLA3* CG/GG: 12.71 months ±3.5 (95% CI: 5.7–19.7) vs. CC: 18.3 months ±3.6 (95% CI: 11.2–25.4); $p = 0.04$
Mandorfer 2018 [16]	*N* = 141, MASLD 26.2%, ALD 73.8%, Age 58.6, Male 80%, Austrian: 100% (assumed), Follow-up: Median 27.4 months	All patients with portal hypertension (HVPG ≥ 6)	GG vs. CG/CC: aSHR: 2.1 (1.1–4.0, $p = 0.024$)
PNPLA3: HCC			
Grimaudo 2020 [38]	*N* = 471, MASLD 100%, Age 49.4, Male 61.6%, Italian: 100% (assumed), BMI: 30.3, DM: 46.1%, Follow-up: Median 64.6 months	Histologic F3-F4	CG/GG vs. CC: HR 2.66 (1.02–7.13) $p = 0.04$
Guyot 2013 [50]	*N* = 279, ALD 100%, Age 56.7, Male 77.8%, French: 100% (assumed), White 100%, Black 0, Asian 0, Other 0, BMI: 27.4, DM 31.2%, Follow-up: 67 months	All patients with cirrhosis	GG vs. CC: HR 1.9 (1.31–2.8) $p = 0.0003$
Nahon 2024 [53]	*N* = 486, ALD 100%, Age 58, Male 68.5, French: 100%, BMI: 27.5, DM: 22.7%, Follow-up: Median 43.7 months	All patients with cirrhosis	CG/GG vs. CC: sHR = 1.52; CI 0.85–2.73; $p = 0.158$
Pelusi 2023 [54]	*N* = 449, MASLD 100%, Age: 62, Male: 58%, BMI: 30, DM: 46%, Follow-up: Median 46 months	Histologic F3-F4	No significant association (no HR reported)
Thrift 2024 [55]	*N* = 591, MASLD 100%, Follow-up: Mean duration between enrollment and HCC development of 2.21 years	All patients with cirrhosis	CG/GG vs. CC: HR 1.68 (95% CI 0.65–4.33)
Urias 2024 [56]	*N* = 732, ALD 18%, Non-viral non-alcohol-associated 56%, Age 57.6, Male 57.4%, White 91.1%, Black 3.9%, Hispanic 1.6%, Asian 3.3%, BMI: 30.9, DM 52.9%, Follow-up: Mean 6.6 years	All patients with cirrhosis	5-year cumulative incidence: ALD: CC/CG vs. GG: 9.7% (5.2%–15.8%) vs. 17.1% (5.2%–35.0%), $p = 0.044$ Non-viral nonalcohol-related liver disease: CC/CG vs. GG: 4.3% (2.3%–7.3%) versus 15.4% (7.5%–25.9%), $p = 0.0001$

(Continues)

TABLE 5 | (Continued)

Study	Cohort	Fibrosis measurement	Findings
PNPLA3: Liver-related mortality			
Grimaudo 2020 [38]	$N = 471$, MASLD 100%, Age 49.4, Male 61.6%, Italian: 100% (assumed), BMI: 30.3, DM: 46.1%, Follow-up: Median 64.6 months	Histologic F3-F4	CG/GG vs. CC: HR 3.64 (1.18–11.2) $p = 0.02$
Mandorfer 2018 [16]	$N = 141$, MASLD 26.2%, ALD 73.8%, Age 58.6, Male 80%, Austrian: 100% (assumed), Follow-up: Median 27.4 months	All patients with portal hypertension (HVPG ≥ 6)	GG vs. CC/CG: aSHR: 2.2 (1.08–4.46, $p = 0.029$)
PNPLA3: All-cause mortality			
Friedrich 2014 [37]	$N = 105$, ALD 100%, Age: 52.6, Male: 74.3%, White: 100%, BMI: 26.7, Follow-up: NA	All patients with ESLD	Survival: CC = 30.7 months ±7.9 (95% CI: 15.1–46.2); CG/GG: 17.1 months ±3.3 (95% CI: 3.3–10.6) $p = 0.012$
Mandorfer 2018 [16]	$N = 141$, MASLD 26.2%, ALD 73.8%, Age 58.6, Male 80%, Austrian: 100% (assumed), Follow-up: Median 27.4 months	All patients with portal hypertension (HVPG ≥ 6)	GG vs. CG/CC: aSHR: 2.2 (1.22–3.98, $p = 0.009$)
TM6SF2: MALO			
Balcar 2023 [67]	$N = 443$, MASLD 22.8%, ALD 77.2%, 91% European, 7% Arabic, 1.4% Asian, 0.3% African, Follow-up: Median 70.8 months	All patients with portal hypertension (HVPG ≥ 6)	CT/TT vs. CC: HR 1.08 (0.80–1.44) $p = 0.62$
TM6SF2: HCC			
Nahon 2015 [68]	$N = 249$ (subset of larger cohort), ALD 100%, French: 100%, Follow-up: 68 months	All patients with cirrhosis	CT/TT vs. CC: HR = 2.49 (1.5–4.5) $p = 0.003$
Nahon 2024 [53]	$N = 486$, ALD 100%, Age 58, Male 68.5, French: 100%, BMI: 27.5, DM: 22.7%, Follow-up: Median 43.7 months	All patients with cirrhosis	CT/TT vs. CC: SHR = 1.66; (0.86–3.19); $p = 0.129$
TM6SF2: Liver-related mortality			
Balcar 2023 [67]	$N = 443$, MASLD 22.8%, ALD 77.2%, 91% European, 7% Arabic, 1.4% Asian, 0.3% African, Follow-up: Median 70.8 months	All patients with portal hypertension (HVPG ≥ 6)	CT/TT vs. CC: HR 0.90 (0.59–1.37) $p = 0.62$
HSD17B13: MALO			
Scheiner 2020 [69]	$N = 202$, MASLD 27.7%, ALD 72.3%, Age 57.14, Male 76%, Austrian: 100% (assumed), Follow-up: Median 26 months	All patients with portal hypertension (HVPG ≥ 6)	T/TA or TA/TA, vs. T/T: HR: 1.18 (0.77–1.82); $p = 0.45$

(Continues)

TABLE 5 | (Continued)

Study	Cohort	Fibrosis measurement	Findings
HSD17B13: HCC			
Kogiso 2023 [52]	$N = 402$, MASLD 84.3%, ALD 15.7%, Age 55, Male 56.7%, Japanese: 100% (assumed), BMI: 26.6, DM: 47.5%, Follow-up: 8.1 years	FIB-4 < 2.67 or ≥ 2.67	Higher incidence of HCC in *HSD17B13* rs72613567--T/T vs. T/TA or TA/TA among those with FIB-4 < 2.67 (approximately 11% vs. 4%; $p = 0.04$), but not FIB-4 ≥ 2.67 (approximately 34% vs. 22%).
Nahon 2024 [53]	$N = 486$, ALD 100%, Age 58, Male 68.5, French: 100%, BMI: 27.5, DM: 22.7%, Follow-up: Median 43.7 months	All patients with cirrhosis	TA/TA or T/TA vs. TT: SHR = 1.45 (0.79–2.66) $p = 0.227$
Scheiner 2020 [69]	$N = 202$, MASLD 27.7%, ALD 72.3%, Age 57.14, Male 76%, Austrian: 100% (assumed), Follow-up: Median 26 months	All patients with portal hypertension (HVPG ≥ 6)	No significant association: TA/TA or T/TA (3%) vs. TT (5%) $p = 0.493$.
HSD17B13: Liver-related mortality			
Scheiner 2020 [69]	$N = 202$, MASLD 27.7%, ALD 72.3%, Age 57.14, Male 76%, Austrian: 100% (assumed), Follow-up: Median 26 months	All patients with portal hypertension (HVPG ≥ 6)	TA/TA or T/TA vs. TT: aSHR: 1.06 (0.6–1.9); $p = 0.83$
HSD17B13: All-cause mortality			
Scheiner 2020 [69]	$N = 202$, MASLD 27.7%, ALD 72.3%, Age 57.14, Male 76%, Austrian: 100% (assumed), Follow-up: Median 26 months	All patients with portal hypertension (HVPG ≥ 6)	TA/TA or T/TA vs. TT: aSHR: 1.18 (0.68–2.04); $p = 0.55$
MBOAT7: HCC			
Nahon 2024 [53]	$N = 486$, ALD 100%, Age 58, Male 68.5, French: 100%, BMI: 27.5, DM: 22.7%, Follow-up: Median 43.7 months	All patients with cirrhosis	CT/TT vs. CC: SHR = 1.83; 0.85–3.94; $p = 0.122$

Note: Unless otherwise specified, effect sizes are shown as subhazard ratio [sHR] or hazard ratio [HR] (95% confidence interval). GG, CG and CC refer to genotype of *PNPLA3*-rs738409. TT, CT and CC refer to genotype of *TM6SF2*-rs58542926. TA/TA, TA/T and TT refer to the genotype *HSD17B13*-rs72613567.

Abbreviations: AF, advanced fibrosis; ALD, alcohol-associated liver disease; aSHR, adjusted subhazard ratio; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; ESLD, end-stage liver disease; FIB-4, fibrosis-4 index; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; kPa, kilopascals; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; VCTE, vibration-controlled transient elastography.

3.7.2 | Fibrosis-4 Index

Two studies (three cohorts) with 55,319 participants compared outcomes by Fibrosis-4 (FIB-4) index [36, 44] (Table 5). For MALO outcomes, in low FIB-4 (<1.3), one cohort ($n=7893$) showed a significant association between *PNPLA3* gene variant and MALO [36], while one cohort from the same study ($n=46{,}880$) showed no association; one did not report effect size in FIB-4 < 1.3 [44]. One study [36] ($n=7893$) showed a significant association between *PNPLA3* gene variant and intermediate FIB-4 index (1.3–2.67). Two cohorts [36] ($n=54{,}773$) showed a significant association between *PNPLA3* gene variant and high FIB-4 index (> 2.67) (sHR ranging from 2.17 to 3.77). One study [44] ($n=546$) showed no significant association between *PNPLA3* gene variant and MALO in FIB-4 > 1.3 [sHR 0.64 (95% CI 0.18–2.28) $p=0.49$].

3.7.3 | Cirrhosis-Only Studies

Ten studies with 3677 participants included only patients with cirrhosis or portal hypertension [16, 37, 50, 53–56, 67–69] (Table 5). Four of these studies [16, 37, 67, 69] ($n=891$) examined MALO outcomes. Two studies assessing *PNPLA3* genotype showed a significantly increased risk [16, 37]; one assessing *TM6SF2* genotype showed no difference [67]; as did one assessing *HSD17B13* genotype [69]. Seven studies [50, 53–56, 68, 69] ($n=3093$) evaluated HCC incidence. Five studies ($n=2537$) assessed *PNPLA3* genotype, with two [50, 56] finding a significantly associated risk, and three [53–55] finding no difference. Two studies [53, 68] ($n=735$) assessed *TM6SF2*, and one found a significantly increased risk of HCC [68] while the other showed no change [53]. Two studies [53, 69] ($n=688$) assessed *HSD17B13*, and both studies found no difference in HCC incidence. One study [53] ($n=486$) assessed *MBOAT7*, and this was found to have no difference in HCC incidence. Three studies [16, 67, 69] ($n=786$) evaluated liver-related mortality based on *PNPLA3*, *TM6SF2*, or *HSD17B13* genotypes. Only the study [16] ($n=141$) assessing *PNPLA3* genotype was associated with significantly increased risk, while there was no difference based on *TM6SF2* [67] or *HSD17B13* [69] genotype. Three studies [16, 37, 69] ($n=448$) evaluated all-cause mortality (censored for liver transplant). Two studies [16, 37] ($n=246$) assessing *PNPLA3* were associated with significantly increased risk; the study on *HSD17B13* [69] showed no association.

3.7.3.1 | Other Subgroup Analyses. Subgroup analyses based on adjusted versus unadjusted HR/sHR values, country of the study (West vs. Asia), pure MASLD versus including ALD patients and steatosis diagnosis method were limited by the small number of studies in each category (Figures S6–S9).

3.7.3.2 | Quality Assessment. Quality assessment using the Q-Genie tool showed overall high quality with moderate to good quality of studies (Table S2). We also used the GRADE system to assess studies quality and bias risk (Table S3). Each outcome was evaluated across five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. Risk of bias was assessed using the ROBINS-I tool (Figure S10). Additional considerations (e.g., large effect size) were applied in select cases.

4 | Discussion

Genome-wide association studies have yielded major insights into the pathogenesis of SLD, yet these findings do not readily translate into clinical practice due to their cross-sectional nature. Here, through meta-analysis of longitudinal outcomes, we have established clinically meaningful risk estimates for patients who have these common variants. Most studies reported that *PNPLA3* and *TM6SF2* risk variants are strongly associated with incidence of liver-related outcomes such as cirrhosis, MALO, HCC and liver-related mortality, with directionally similar but somewhat weaker effects of *MBOAT7* on liver-related outcomes. Overall, this provides evidence toward use of genetic testing in risk stratification in SLD clinics, which can be combined with other clinical risk factors to better characterise disease heterogeneity and predict individual outcomes [71].

The *PNPLA3* risk variant had a large effect on risk of MALO and liver-related mortality, with HR > 2 for rs738409-GG versus rs738409-CC genotype. Notably, this sub hazard ratio for MALO risk is similar to that of type 2 diabetes [72, 73], which is a well-recognised risk factor described in clinical practice guidelines [74, 75]. The association between *PNPLA3* genotype and MALO or liver-related death was stronger in patients with more advanced liver disease. These results are consistent with existing literature that while genotypic information may have only a marginal effect in the general population [76], it may be more informative in the higher-risk patients based on fibrosis stage or FIB-4 [12, 36, 47]. Based on these findings, *PNPLA3* genotyping may improve risk stratification in individuals deemed to be at higher risk based on histologic fibrosis stage or FIB-4 score and routine testing may be warranted in this setting.

Overall, we found little evidence for association between these risk alleles and extrahepatic endpoints. The exceptions were the borderline significant association between the *PNPLA3* risk allele and increased overall mortality, likely driven by increased liver-related mortality, or between *MBOAT7* and decreased overall mortality in two small studies [15, 62]. There have been conflicting results in the literature regarding associations between *PNPLA3* and *TM6SF2* risk alleles and cardiovascular mortality. Both liver disease-promoting alleles *PNPLA3*-rs748309-G and *TM6SF2*-rs58542926-T are associated with decreased triglyceride and low-density lipoprotein levels but also with increased risk of type 2 diabetes, with small effect sizes for the *PNPLA3* variant but much larger effect sizes for the *TM6SF2* variant [3, 7]. Thus, depending on the population and prevalence of cardiovascular risk factors and baseline risk of liver disease as a competing risk, effects on cardiovascular outcomes may go in either direction. We note also the relatively modest effect size on lipids for the *PNPLA3* risk variant and limited power for the *TM6SF2* variant (which has a much lower allele frequency): we recently found in the general population that those with the homozygous *TM6SF2*-rs58542926-TT genotype (<1% of the overall population) had reduced risk of major adverse cardiovascular events compared to wild-type rs58542926-CC [3], but existing SLD cohorts are likely too small to detect such an association. The *MBOAT7*-rs641738-TT genotype is associated with an increased incidence of cirrhosis and HCC compared to the *MBOAT7*-rs641738-CC genotype, while also apparently being associated with a lower risk of all-cause mortality, though this

finding was based on only two relatively small studies. It is unclear what underlies this difference in mortality.

Our study highlights key limitations of the existing literature. First, almost no studies assessed whether genetic variants predict clinical outcomes after stratification by disease stage determined by imaging-derived non-invasive tests such as vibration-controlled transient elastography [77, 78]. This will be increasingly notable as these imaging-based tests have been endorsed in clinical guidance documents and are largely replacing liver biopsy for routine risk stratification [74, 75, 79]. Second, the bulk of the literature focused on *PNPLA3* and to some extent *TM6SF2* variants, with sparse literature on other variants. One potential explanation is that effects of these variants are not being reported because they have little to no effect on MALO and other clinical outcomes [36]. Third, most studies were on MASLD. By contrast, fewer studies assessed alcohol-related liver disease, and we did not identify any that reported results in patients with MASLD and increased alcohol intake (MetALD). This population has been described in the literature as separate from MASLD alone, and the long-term outcomes in this group remain less well understood [80]. Most studies included patients both with and without cirrhosis, which is particularly relevant for HCC outcomes where underlying disease severity crucially impacts incidence. Most studies were retrospective rather than prospective, which may limit characterisation of exposures and risk factors before the onset of disease, thereby reducing potential sources of bias and confounding that are often found in case–control studies [81]. Finally, reporting of endpoints was inconsistent, with some studies reporting 5-year cumulative incidence and others reporting HR/sHR, and some studies pooling genotypes (e.g., *PNPLA3*-rs738409-GG/CG vs. CC) but others reporting dosage effects or comparing individual genotypes. We suggest that consistent reporting of outcomes including both subhazard/hazard ratios and 5- or 10-year cumulative incidence for individual genotypes, and stratification by disease severity (histology, elastography and/or FIB4) would improve interpretability of the literature and facilitate future meta-analyses.

Several limitations should be noted in our study. The inconsistent reporting of endpoints that we highlighted earlier may have resulted in non-representative estimates of effect sizes in the meta-analysis. There was also a significant overlap in patient populations and the use of similar biomedical databases across studies (especially UK Biobank) which presented challenges in including all study data. To minimise redundancy, we prioritised those with the largest patient cohorts in meta-analyses. However, this approach may have inadvertently excluded smaller but otherwise high-quality studies. Our study also was not able to analyse the interactions between different combinations of these genetic variants and was only designed to observe their effects in isolation.

In summary, SLD-associated genetic variants, especially in *PNPLA3* and *TM6SF2*, were associated with markedly increased morbidity in patients with SLD. We believe there is sufficient evidence to recommend genotyping to improve risk stratification in SLD patients with advanced liver disease and enable future interventions on these variants to alter clinical outcomes in specific SLD populations [82, 83].

Author Contributions

Matthew Kubina: conceptualization, methodology, investigation, writing – original draft, writing – review and editing, visualization, formal analysis, data curation. **Vitchapong Prasitsumrit:** writing – original draft, writing – review and editing, formal analysis, data curation. **Jarell Tan:** writing – review and editing, data curation, formal analysis. **Joo Wei Ethan Quek:** data curation, formal analysis, writing – review and editing. **Dhiraj Peddu:** writing – review and editing, data curation, formal analysis. **Ankit Mishra:** writing – review and editing, formal analysis. **Pojsakorn Danpanichkul:** writing – review and editing, formal analysis. **Jake P. Mann:** writing – review and editing, formal analysis. **Eric Trépo:** writing – review and editing, formal analysis. **Stephan Buch:** writing – review and editing, formal analysis. **Daniel Q. Huang:** writing – review and editing, formal analysis. **Cheng Han Ng:** writing – review and editing, formal analysis. **Mark D. Muthiah:** writing – review and editing, formal analysis. **Yu Jun Wong:** writing – review and editing, formal analysis, investigation. **Karn Wijarnpreecha:** writing – review and editing, conceptualization, investigation, methodology, data curation, formal analysis, supervision. **Vincent L. Chen:** conceptualization, methodology, data curation, investigation, formal analysis, supervision, writing – review and editing, writing – original draft, visualization, resources.

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Conflicts of Interest

V.L.C. received grants (paid to University of Michigan) from AstraZeneca, KOWA and Ipsen. E.T. received research and travel support from Gilead. D.Q.H. served as a speaker for Gilead and Roche. M.D.M. has served as a consultant to Roche, Estella and Gilead; has been an advisor for Lerna Bio; and has received payment for speaking at Boston Scientific, Olympus Medical, Roche and Astellas. C.H.N. consulted for Boxer Capital and is the CEO of LiverGENIX.

Data Availability Statement

The data that supports the findings of this study are available in the Supporting Information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.